Measurement of anaesthetic vapour concentration under clinical conditions.

Estall, Penelope Mary

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Measurement of Anaesthetic Vapour Concentration

Under Clinical Conditions

Submitted by Penelope Mary Estall

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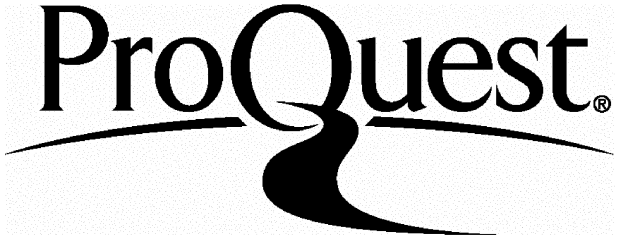

Summary

It is shown that there is a need for a versatile inhalation anaesthetic meter. In particular it is necessary if fully closed circuit anaesthesia, which saves anaesthetic expenditure and reduces theatre pollution, is to be used. The need has not been met by any of the available meters, with the possible exception of the Emma (an instrument made by Engstrom) which is new and unproven.

Various methods of determining the concentration of any anaesthetic against a variable concentration of the other anaesthetic circuit gases are examined. Of these gas chromatography, adapted to give a separation in less than 15 seconds and components selected for use in the operating theatre, appears the most promising.

A laboratory prototype is built and the selection of the component parts is described. A solenoid operated gas sampling valve and a refractometer detector are developed. This model satisfactorily separates halothane, penthrane or ethrane from the other anaesthetic circuit gases in the required time. Other anaesthetic agents were not tried, but it is expected that they would behave similarly with the possible exception of cyclopropane, the lightest and at normal temperatures and pressures the only gaseous potent anaesthetic agent. The operating conditions of the chromatograph are determined.

The modifications that would be required to adapt the laboratory model into a clinical instrument are discussed, and the conclusion drawn that this system could form the basis of a satisfactory instrument.

Acknowledgements

Many people have helped me to produce this thesis. I would have liked to record my appreciation of all of them individually, however, that is not possible so I hope they will accept my thanks in this form.

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Abbreviations

atm	atmospheres
cc	cubic centimetre
cc/min	cubic centimetre per minute
cm	centimetre
C	celsius
CMOS	a logic family
DC or dc	direct current
EMMA	Engstroms Multigas Monitor for Anaesthesia
FET	field effect transistor
HMSO	Her Majesty's Stationery Office
hr	hour
in or "	inch
K Ω	10^3 ohms
lbf/in^2	pound force per square inch
l/min	litre per minute
mA	milliampere
MAC	minimum aveola concentration
min	minute
ml	millilitre
ml/min	millilitre per minute
mm	millimetre
mm Hg	millimetres of mercury
m/sec	metre per second
M Ω	10^6 ohms
NC	normally closed
NIOSH	National Institute for Occupational Safety and Health
nm	nanometre
NO	normally open

Nsm^{-2}	Newton seconds per metre squared
Op amp	operational amplifier
S	second
STP	Standard Temperature and Pressure
TTL	Transistor, Transistor Logic
V	volt
vs	versus
v/v	volume per volume
+ve	positive
-ve	negative
μF	10^{-6} Farads
o	degrees

Symbols

A	eddy diffusion constant
B	diffusional spreading coefficient
C	resistance to mass transfer coefficient
df	thickness of liquid layer
Di	diffusion coefficient in the liquid phase
dH	change in height equivalent to a theoretical plate
$d\overline{U}$	change in average carrier gas velocity
H	height equivalent to a theoretical plate
Hmin	minimum value of height equivalent to a theoretical plate
K	partition coefficient
m	sample volume
N	plate number
p	statistical confidence level
Q_E	quantity of sample eluting
Q_{N+1}	quantity of sample in $N + 1^{th}$ plate
r	volumes of carrier-gas added
th	time from sample introduction to halothane peak
ti	time from sample introduction to start of nitrous oxide elution
tn	time from sample introduction to nitrous oxide peak
$\overline{U}$	average carrier-gas velocity
$\overline{U}$min	minimum value of average carrier-gas velocity
Vout	voltage output
y	proportion of sample in liquid phase
z	proportion of sample in gas phase
zair	proportion of air in gas phase
zanaesth	proportion of anaesthetic in gas phase

z_h	proportion of halothane in gas phase
z_n	proportion of nitrous oxide in gas phase

CHAPTER 1

1 Introduction

This thesis is concerned with all aspects of the development of a meter for routine clinical measurement of the concentration of patient inhaled anaesthetic.

The first aspect covered is an examination of the need for such an instrument. Having decided that there is a place for an anaesthetic concentration meter the qualities required are defined. Available meters and transducers can then be compared with the requirements to determine if the need has already been met elsewhere. As no meter was found to be entirely suitable, with the possible exception of the Emma, study of methods of measuring the concentration was conducted, a particular method (gas chromatography) was selected and the results obtained with this method were examined.

The following chapters cover these points in depth. A brief description of each is given here in order that the form of the thesis may be grasped before the details are explored.

1.1 The Need for an Anaesthetic Measuring Device

General anaesthesia, with which we are concerned, involves inhalation of anaesthetic agents. The patient is supplied with the anaesthetic, together with oxygen and nitrous oxide, through an anaesthetic circuit from an anaesthetic machine. The anaesthetic circuit is the collection of hoses and components that the patient breathes through. The circuit elements may be configured in a number of ways to give different circuits. It is shown that the fully closed circuit, in which all the patient's breath is rebreathed, has a number of advantages. These include a low fresh-gas flow-rate with inherent saving in the expenditure of anaesthetic circuit gases, low waste-gas flow-rate and a consequential reduction in pollution of the theatre. Controversy

exists regarding the effect of prolonged exposure to trace levels of anaesthetic on the health of anaesthetists.

The disadvantages include an unknown concentration of gases in the anaesthetic circuit and the need for a carbon dioxide absorber.

In any circuit it is necessary to know the level of anaesthesia. This may be achieved by clinical observation of the patient, or by using a technique that provides a known concentration of anaesthetic, or by measuring the concentration. Measurement supplemented by observation is thought to be the most satisfactory under closed circuit conditions.

1.2 Qualities of an Anaesthetic Meter

The meter is required to measure the concentration of anaesthetic against a background of a variable concentration of the other anaesthetic circuit gases when it is used in closed circuits. That is the meter should be unaffected by the composition of the other gases, but ideally it should be sensitive to various anaesthetic agents.

The response of the instrument should be fast with zero drift. The need for frequent calibration is to be avoided. If the meter fails it should do so to an electrically safe state; the anaesthetist should know it has failed so that falsely low readings are never acted on. The meter needs to be easily read and unambiguous.

The meter should work from electricity alone as other services are unlikely to be readily available.

To withstand the operating theatre environment the meter should be robust and should be reasonably small to fit on an anaesthetic trolley.

1.3 Available Meters

Of the meters and transducers examined only the mass spectrometer, Emma, and improved ultraviolet meter were found to be able to make

measurements of anaesthetic concentrations satisfactorally in closed circuits. The difficulty of measurement lies in the anaesthetic vapour being in a variable composition of the other circuit gases. The use of a mass spectrometer for routine measurement is extravagent. Of the various anaesthetic agents the improved ultraviolet meter is sensitive only to halothane. The Emma is new and undergoing clinical trials at present. So there is no device proven wholly suitable.

1.4 Methods of Measurement

Physical methods of measurement were examined but it proved impossible to find one which would provide the concentration directly without interference from the other anaesthetic circuit gases. So methods of separating the gases were explored. Filtering was ruled out since the anaesthetic is absorbed onto the filtering material which eventually becomes saturated and requires reactivation. Gas chromatography proved the most appealing since the anaesthetic does not remain on the column permanently so the column will not require frequent attention.

1.5 Gas Chromatography

This is a way of separating small samples of a gas mixture. A carrier gas (the mobile phase) passes through a column which consists of a liquid (the stationary phase) coated onto a fine solid support to give it a large surface area, packed into a glass or stainless steel tube. A narrow sample of the gas to be analysed is introduced into the carrier gas stream. As the sample passes through the column it will spend some time in the liquid phase and some in the gas phase. The sample is separated by the constituent gases spending different proportions of their time in the 2 phases. A gas that spends a smaller proportion of its time in the stationary phase will travel through the column faster than a gas which spends a larger proportion.

The gas coming off the column (the elutant) is sensed by a detector which measures a quality of the gas. The output of the detector is usually an electrical signal which is recorded on paper.

Thus the main parts of a gas chromatographic instrument are a gas sampling valve which introduces the sample into the carrier gas stream, the column which performs the separation and the detector which senses the elutant.

Gas chromatography is generally employed as a laboratory technique taking a long time to separate similar compounds. To use it for a meter requires adaption.

1.6 Modifications required to adapt Gas Chromatography to routine clinical use

Gas chromatography is to be used only as a tool to separate the gases. It will make available the anaesthetic alone in order that any method which can detect the anaesthetic in the carrier gas can then be used, without fear of interference from the other anaesthetic circuit gases. We require a fast separation repeated automatically, selection of the anaesthetic peak, detection and display of the anaesthetic concentration on a meter movement.

By comparison with the usual practices the changes required are shown.

1.6.1 Sample valve

The sample is often injected onto the column by inserting a syringe through a rubber septum into the carrier gas stream. This would obviously not be a satisfactory method of sample introduction for an automated instrument.

Some automated gas sampling valves are available, but none were considered satisfactory owing to the small sample volume required and the materials used in their construction which could be affected by

the anaesthetic agents.

A sampling valve was developed which used 6 solenoid operated valves to connect the sample loop alternately between the carrier-gas supply and column, and between the sample-gas and vent. This proved to be satisfactory.

1.6.2 Detectors

The most commonly used detector is the flame ionisation detector, but the use of a naked flame must be avoided. Other detectors were unsatisfactory for a variety of reasons, so a detector based on measurement of the refractive index of the elutant was developed.

1.6.3 Fast Separation

In laboratory chromatography the desired speed is often achieved by use of elevated temperatures. The clinical instrument will have to operate at a low temperature, but may be thermostated up to about 30 ^{o}C, which is still reasonably low by chromatographic standards.

It is only necessary in this application to separate the anaesthetic from the other anaesthetic circuit gases, that is, there is no need to separate the other gases from each other. By suitable choice of column material, a short column and carrier-gas flow-rate the required separation may be achieved.

1.6.4 Recording

Generally the result of a gas chromatograph separation is a permanent recording on paper of the changes in the parameter being observed. In this case what is required is that the concentration of anaesthetic is displayed on a meter. The anaesthetist will not want to interpret a trace to determine the concentration himself. So electronic circuitry is developed which selects a peak of interest and either the peak height or area of the peak is measured and stored by

analogue means. The stored value is displayed, and the display is refreshed each time a fresh peak of interest is eluted.

So from the usually slow laboratory instrument doing special separations, the chromatographic instrument is to be turned into a fast, repetitive, automatic clinical instrument.

1.7 Experimental Results

The results achieved with a short column proved to be satisfactory, with a separation of the anaesthetic agent from the other anaesthetic circuit gases occuring in about 15 seconds repetitively at room temperature.

1.8 Further engineering development needed

The optimum flow-rate of carrier-gas and the other column parameters have been determined so a prototype can be built which may be used in clinical trials.

As previously stated, the instrument should only require mains electricity so the development of a pump system to provide the carrier gas from room air is required.

The sample-valve electronics will require modification to change from the controllable repetition rate to a fixed rate as variation will not be needed. Sampling of the detector output can easily be automated at the same time.

Obviously the elements which make up the laboratory prototype model will need to be physically rearranged to fit into an instrument case. When this is done the column should be mounted vertically to ensure that the column packing does not settle, leaving a space running the length of the column.

The form of the thesis has now been presented very briefly. So let us start to examine the details by considering the need for an anaesthetic measuring device.

CHAPTER 2

2. The Need for an Anaesthetic measuring device

The purpose of this particular chapter is to demonstrate the need for an anaesthetic concentration meter. To this end brief descriptions of various aspects of the anaesthetic field are included. These descriptions start with a basic definition of anaesthesia and proceed from this to anaesthetic machines through various anaesthetic circuits to one particular circuit (the fully closed). The conditions under which the instrument would work are discussed, together with the role it would play.

2.1 Anaesthesia

Anaesthetics are used to render patients insensitive to pain during surgical operations. Anaethesia may be either local or general. Local anaesthesia is produced by drugs which block the transmission of information along nerve fibres. General anaesthesia, on the other hand, interrupts the central nervous system's ability to assimilate, integrate and respond to noxious stimuli. We are concerned here only with general anaesthesia.

2.2 General Anaesthesia

General anaesthesia causes loss of consciousness, muscle relaxation and pain relief. Anaesthesia is commonly produced by a combination of drugs, principally one specific pharmacologic agent for each component of the anaesthetic experience. Thus, if deep anaesthesia is required, loss of consciousness and analgesia may be produced with an injection of a barbiturate and inhalation of a mixture of nitrous oxide, oxygen and halothane. Muscles may be relaxed by using a neuro-muscular blocking drug such as curare.

2.3 Nature of Inhalation Anaesthesia

The inhaled anaesthetic passes from the lungs into the blood circulation and thence to the brain. The amount of anaesthetic in the blood produces several distinct stages of anaesthesia. The first phase is analgesia, or absence of pain, the second stage is mental or physical excitement. In the third stage called the surgical stage complete loss of consciousness is accompanied by muscle relaxation. Swift progress to the third stage is required since it is undesirable to remain in the second stage.

If too much anaesthetic is administered and the blood concentration is excessive respiration and circulation may become depressed or stop entirely. This is because the anaesthetic affects the specific brain centres concerned with controlling circulation and respiration. It is necessary, therefore, to know the level of anaesthesia at all times.

2.4 Determination of the level of Anaesthesia

The level of anaesthesia may be determined by use of one of three methods. It may be judged by physiologic observation of the patient. That is, for example, changes in the pulse strength and rate, blood pressure, or depth of breathing (in spontaneously breathing patients) may be observed and from these the depth of anaesthesia may be judged.

The other two methods rely on knowing the concentration required. This concentration may be obtained by using a technique that delivers known concentrations such as the use of a calibrated vapouriser where none of the expired gas is rebreathed. Alternatively, the concentration may be determined by measurement, in which case a technique which would otherwise give an unknown concentration may be used.

2.5 Scope of the Meter Under Consideration

The meter will be used only in general anaesthesia where inhalation anaesthetic agents such as nitrous oxide, halothane, enflurane, etc, are

used, and will only measure the concentration of the vaporized anaesthetic agent. Other gases in the anaesthetic circuit may include; oxygen, nitrogen, nitrous oxide, carbon dioxide and water vapour. Meters to measure the concentration of these gases are beyond the scope of this thesis, although, they are covered briefly to provide some indication of the needs for development in this field.

2.6 Delivery of Anaesthetic Circuit Gases

The gases that the patient breathes are supplied from bottles at high pressure (up to 3,000 lbf/in^2), or from piped supplies (60 lbf/in^2) through the anaesthetic machine and associated vaporizer, through the anaesthetic circuit to the face mask, endotracheal tube or tracheotomy connection at low pressure (between 0 and 60 lbf/in^2).

The anaesthetic machine and anaesthetic circuit discussed below are separated, although in practice it would be impossible to have one without the other since the anaesthetic machine houses all the component parts, and the anaesthetic circuit is the way in which these parts are interconnected.

2.7 Anaesthetic Machines

The anaesthetic machine is generally a trolley on which are mounted the gas bottles, oxygen, nitrous oxide and carbon dioxide, pressure regulators and cylinder yokes or the pipeline connectors. The gas supplies are connected by valves to the flow meters and the gases mix together in the hose supplying the anaesthetic circuit. Other items that may be on the trolley include vaporizer , carbon dioxide absorber, reservoir bag, oxygen meter, ventilator, humidifier and non-return valves.

The anaesthetic machine's principle job is to provide a known gas composition, but it also physically supports all the other components necessary to deliver the gases to the patient, all that is except the tubing that links the components together and forms the anaesthetic circuit.

2.8 Anaesthetic Circuits

Anaesthetic circuits consist of the assembly of hoses and components through which the patient breathes. It is supplied with fresh gas and anaesthetic vapour or fresh gas alone. These are at low pressure, come from the anaesthetic machine and are delivered to the patient. The fresh gas consists of a mixture of oxygen, nitrous oxide and carbon dioxide. The desired composition of the mixture is set by adjustment of the flow-rates of the various gases which are indicated on the anaesthetic machine. The total volume of gas flowing per minute is of interest as this is one of the factors that determines whether rebreathing will take place. The other factors which determine whether any rebreathing occurs, and if so how much, include the patient's minute volume, patient's anatomical dead space, the respiratory flow pattern and duration of the expiratory pause.

2.9 Classification of Anaesthetic Circuits

Anaesthetic circuits may be classified in a number of ways. The way favoured by Hill (1976) classifies according to the amount of rebreathing that occurs. There are four types of circuit in the Hill classification:

1) Open, where no rebreathing takes place.

2) Semi-open, where some rebreathing takes place, though insufficient to cause carbon dioxide to build up.

3) Semi-closed, where more rebreathing takes place which would cause the carbon dioxide to build up if a carbon dioxide absorber was not used.

4) Fully-closed, where all the gas is rebreathed and fresh gas is supplied at a very low flow-rate to replace that consumed or lost.

To complete the classification there are two types of fully-closed system. One with the vaporizer in the rebreathing circuit (VIC), and the other with the vaporizer outside the rebreathing circuit (VOC).

It is interesting to note that all the circuits have almost the same, or very similar, component parts; it is mainly the way in which these parts are connected that creates the different circuits. The points of commonality are:

1) a source of oxygen,which in the simplest case is atmospheric,

2) a source of anaesthetic gas and/or a vaporizer for volatile anaesthetic agents,

3) a method of carbon dioxide elimination either by venting to atmosphere, or by chemical absorption (usually using soda lime), or both,

4) all systems except the open also make use of a reservoir to contain the high peaks of flow. The open system usually uses an on demand gas-flow so that the high flow-rate is not constant, but delivered when required.

The way in which these are configured to give the different circuits is shown in Figure 2.1.

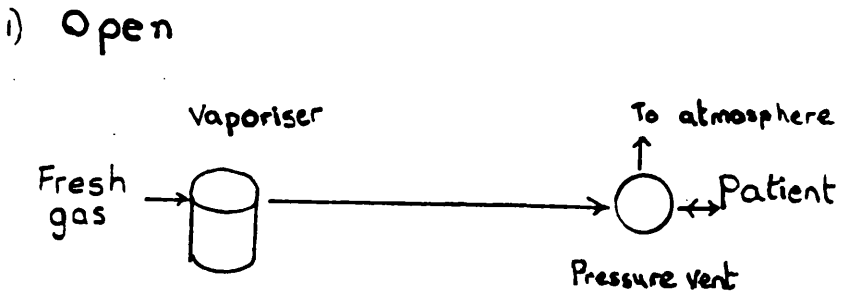
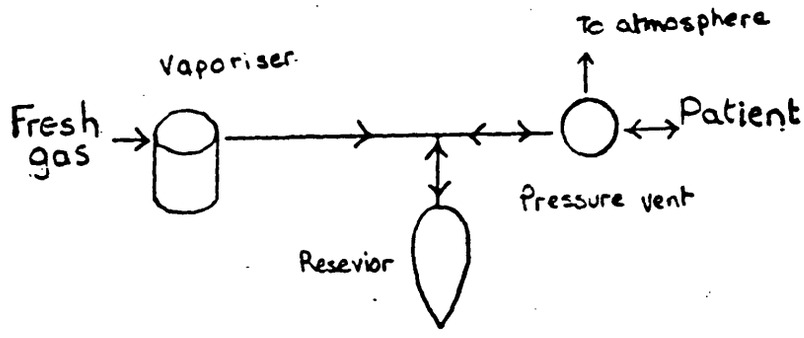
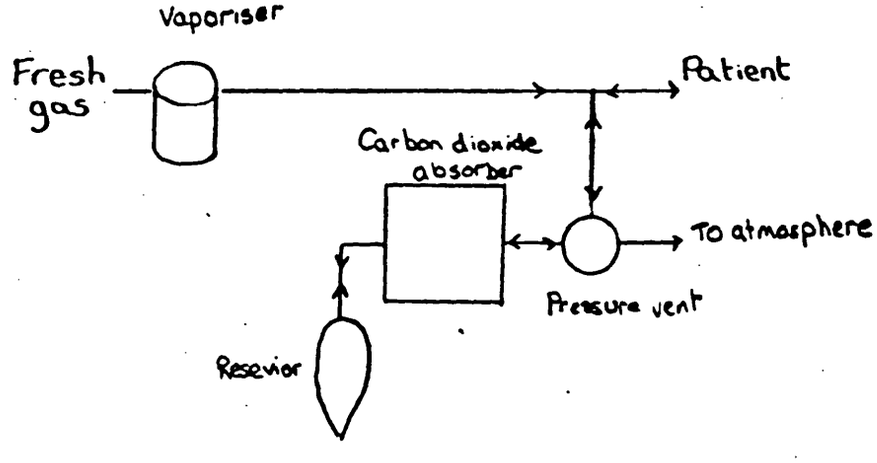


Figure 2.1

2) Semi-open



3) Semi-closed

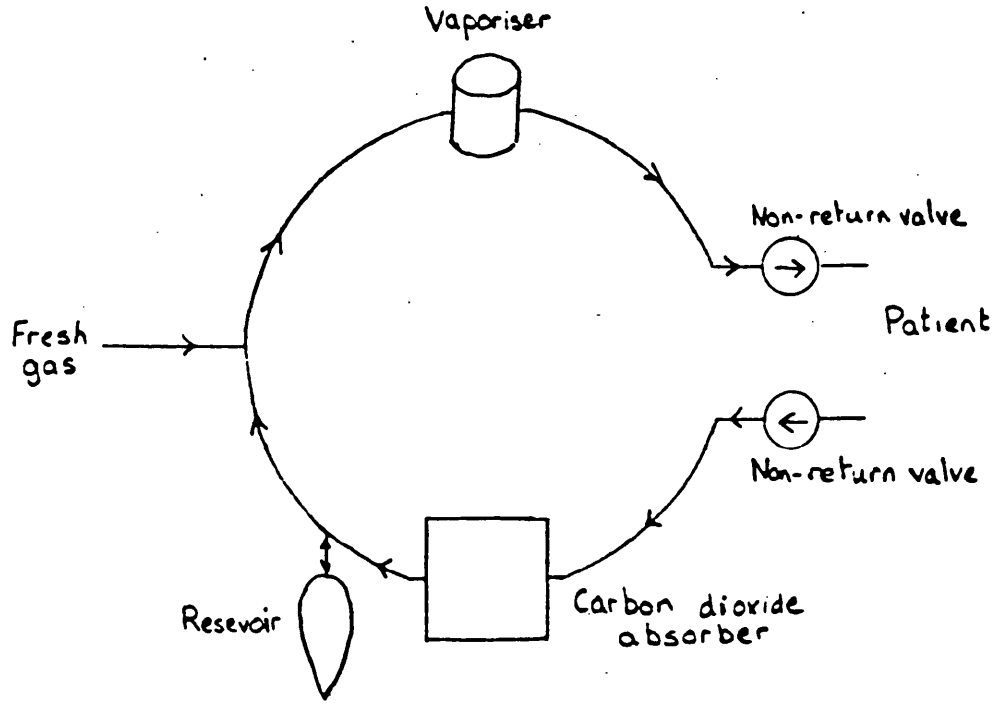


→ indicates direction of gas flow

Figure 2.1 cont

4) Fully closed

a) Vaporiser in circuit (VIC)



b) Vaporiser outside circuit (VOC)

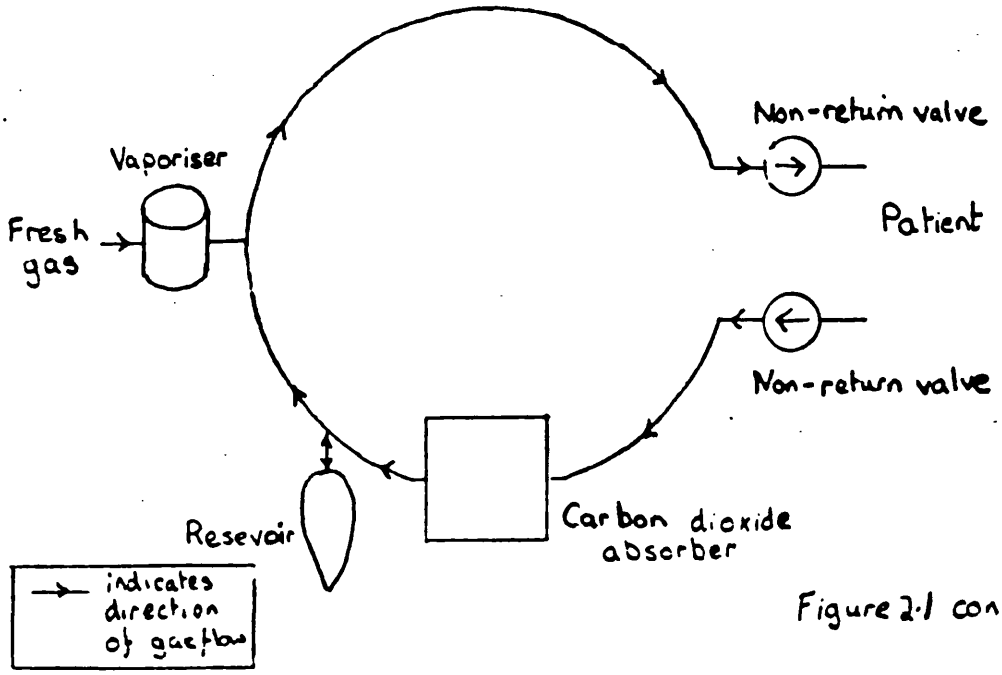


Figure 2.1 continued

Thus in the open system fresh-gas passes through the vaporizer to the patient on demand. During expiration the pressure-vent opens and the patient's expirations are expelled from the circuit, either into the operating theatre, or ducted away. High flows of fresh gas on demand are required to accommodate the patient's peak inspiration rate.

In the semi-open system the fresh-gas flow-rate is lower as the reservoir may fill with the fresh-gas, and some of the expired-gas, during the expiratory phase. This is then available during inspiration. The semi-closed system recycles more of the patient's breath, and a lower fresh-gas supply-rate is used. The patient's breath passes through the carbon dioxide absorber and into the reservoir. Excess pressure is relieved by the pressure-venting-valve. Inspired-gas is drawn from both the reservoir and the fresh-gas supply.

Finally in the closed circuit the gases circulate, the patient inspires from the low fresh-gas supply and reservoir, and expires through the carbon dioxide absorber into the reservoir. The vaporizer may either be in the circuit, or in the fresh-gas supply.

2.10 The Role of a Meter

Consider again the open circuit, the composition of the mixture of gases given to the patient is known within acceptable limits. This is because known flow-rates of the gases are set up on the anaesthetic machine. Also, vaporizers are well developed and so deliver the set concentration over a wide range of temperatures and flow rates. The patient breathes only these gases so, as there is no uncontrolled gas concentration, there is no need for further routine measurement. The flow-rate meters and the setting of the vaporizer define the concentration sufficiently. However, in the case of the semi-closed and fully-closed circuit the concentration is not immediately apparent. Consider if a fully-closed system were leak free and that the patient did not consume any of the

anaesthetic; also that none of the anaesthetic were absorbed by the rubber hoses, then when a desired anaesthetic plane had been reached, the vaporizer could be switched off and the depth of anaesthesia would be maintained by the anaesthetic rebreathed. However there are leaks (Berner 1973) and anaesthetic is absorbed by the hoses (Eger, Larson and Severinghaus 1962). During induction and until equilibrium is reached the inhaled-anaesthetic is absorbed by the patient, that is, more anaesthetic enters the blood than leaves it. The rate at which this happens is discussed by Mapleson (1962). At equilibrium the patient does not consume any anaesthetic although some may be lost through the skin. So to maintain a particular level of anaesthesia some anaesthetic must be added to the circuit to balance that lost. However, extreme care must be exercised to ensure that not even a slight excess of anaesthetic over that lost is given, as over a period of time the concentration of anaesthetic could build up to a fatal level.

Thus in the open-circuit the concentration of anaesthetic is reasonably well known, but in the closed-circuit the concentration is unknown as a balance between the anaesthetic lost and anaesthetic input must be obtained and the anaesthetic loss is unknown. So it is only in the closed and semi-closed circuit that the concentration is unknown and only there that a means of measuring the anaesthetic depth is needed. A meter that would measure the concentration of anaesthetic in a closed or semi-closed system should be able to measure the concentration in open or semi-open if required.

Thus as the need for some means of measuring the anaesthetic-depth has been demonstrated in closed-loop anaesthesia, then to decide if a meter is necessary one must decide that closed-loop anaesthesia is desirable. There are other methods of determining the level of anaesthesia apart from measuring the concentration of anaesthetic that the patient is breathing, so first we will examine the advantages and disadvantages of closed-loop

anaesthesia and, having established its merits, go on to show that a meter is the best solution.

2.11 Advantages of Closed-Loop Anaesthesia

Closed-loop anaesthesia is a low fresh-gas supply system. At equilibrium fresh-gases flow at a rate equal to the losses in the system, that is losses by absorption by rubber hoses, absorption by the patient and leaks. Carbon dioxide which is expired by the patient is removed by being passed through an absorber. The patient rebreathes the treated gas so that the fresh-gas supply is very low, about 300 ml/min in the closed loop system, compared with an extreme flow-rate of 2 to $2\frac{1}{2}$ times the patient's minute volume (average adult 6 L/min), that is up to 15 L/min in a T piece system (Hill (1976)). Similarly the amount of anaesthetic introduced is low. Barton and Nunn (1975) employed a circuit that was not fully closed and used 0.5 L/min nitrous oxide and 0.5 L/min oxygen compared with 5 L/min nitrous oxide and 2 L/min oxygen in a particular semi-open circuit (Magill). The expenditure of halothane after 50 mins in the semi-closed system was 2.9 ml, compared with 15 ml in the Magill circuit (7 L/min 1% halothane). A considerable saving in the gases and anaesthetic-vapour, at worst for the oxygen a saving of 75%. Barton and Nunn state that while this saving is not sufficient to be significant in the U.K it could put the more expensive, but safer inhalation agents such as halothane within reach of third world countries, provided additional expenses to cover such things as absorbers, did not account for all the savings in gas expenditure. This is to be contrasted with an editorial comment in "Contoversy in Anesthesiology" Eckenhoff (1979) which states that administration of anaesthetic in low-flow systems would save $100,000,000 annually presumably in the United States alone although this is not stipulated, nor is the method of calculation.

By the nature of a closed-loop circuit it as a low fresh-gas system so

little gas is allowed to escape into the operating theatre so there is a considerable reduction in atmospheric pollution. Operating theatres in this country are generally equiped with air-conditioning which changes the air in the operating theatre and vents it to the outside. Scavenging may also be employed; this consists of actively sucking waste gases from their expected source and venting to the outside. Both of these methods reduce the quantity of pollution in the theatre, but to keep pollution at a specific level when an open circuit is employed will require far more air changes per hour, and more gas to be pumped away by the scavenger, than if a closed-loop system with its low waste-gas flow-rate were employed. Additional efforts may be made to reduce pollution. These include use of gas-tight equipment, leakage preventative maintenance and air monitoring (Cohen 1980). The concentration of waste anaesthetic is not constant throughout the theatre as hot spots occur,generally these are close to the sources of pollution which tend to be near the anaesthetist.

There is considerable controversy regarding the effects of prolonged exposure to low concentrations of anaesthetic agents, both the short term effects and long term effects.

2.11.1 Long term effects of Exposure to Waste Anaesthetic

The source of the controversy particularly with regard to the long term effects is the difficulty of finding a suitable unexposed control group, to receive a high response rate to surveys and since 1970 (when reports of possible health hazards began to be noticed) to eliminate bias in reporting. Ferstandig in Eckenhoff (1979) lays down some guide lines of pitfalls to avoid in future surveys. He suggests very careful choice of control groups and the use of low values of statistical confidence level ($p = 0.01$). He dislikes the use of questionnaires, prefering medical records and states that retrospective studies with their reliance on memory are less satisfactory than prospective studies. To determine

conclusively the effects of waste anaesthetic these points should be observed.

It should be noted that anaesthetics are not the only contaminant in the operating theatre. Others include x-radiation,freon gas used as a propellant, halogenated hydrocarbons applied as defatting agents and volatile products generated during the preparation of surgical cements (Cohen 1980). Work in the operating theatre is stressful, demanding good concentration. To find a meaningful control-group who are subject to the same working conditions and demands as the anaesthetist, but not exposed to the anaesthetic, is no easy task. However, in the case of dentists some use inhalation anaesthetics in their practice, while others confine themselves to intraveneous sedatives and local anaesthetics, though otherwise their work is similar. Cohen (1980) has a paper in preparation on the effect of anaesthetic exposure on the health of dentists.

The possible deleterious effects of occupational exposure to anaesthetic agents were first reported by Vaisman (1967). This study describes in considerable detail the adverse working conditions and associated health problems of Russian anaesthetists. It also suggested a link between spontaneous abortion and anaesthetic practice, though her survey was not designed specifically for this purpose. Publication of this report generated considerable interest in health problems associated with occupational exposure to anaesthetic gases. In the past decade some twenty epidemiologic surveys in eight countries have been carried out, and in excess of 300 published reports involving problems associated with waste anaesthetic.

Cohen's book "Anesthetic Exposure in the Workplace" (1980) gives an extensive survey of work done to date. This taken in conjunction with A A Spence (1980) article in General Anaesthesia entitled "Chronic exposure to trace concentrations of anaesthesia" and the two sides of the argument

presented in "Controversy in Anaesthesia" Eckenhoff (1979), together with Ferstandig (1978), provide a balanced view of current thinking. Both Cohen and Spence are cautious, but they agree that convincing evidence exists that there is an increased risk of spontaneous abortion among exposed females. Cohen goes further to say that there is indication of increased risk of congenital deformation associated with maternal and/or paternal exposure, and an increased incidence of liver disease in operating theatre personnel. One of the large studies examined was that of Spence, Cohen and Brown (1977) which compared three studies, two in the U.K (Knill-Jones et al 1972, 1975) and one in the U.S (Cohen et al 1974). The conclusions drawn from the comparisons are presented here despite Ferstandig's doubts in "Controversy in Anaesthesia" Eckenhoff (1979), concerning the epidemiologic validity of combining different age groups, practices, countries and control groups. However, he does conceed that lower values of p are achieved because of the increased population.

There was considerable agreement in the conclusions drawn in the comparative paper despite the differences in survey methods, statistical analysis and population base. Exposed female anaesthetists showed a statistically significant miscarriage rate to the unexposed control physicians (16.7% vs 13.3%). Similarly the congenital abnormality rate of children born to exposed females was significantly greater than those born to the unexposed group (5.5% vs 4.0%). Although there was no significant increase in spontaneous abortion among the wives of exposed male anaesthetists, the incidence of abnormalities of children born to exposed males was significantly greater than to the children of the unexposed physicians (5.0% vs 3.7%). Thus, though cautious, Cohen and Spence agree that anaesthetic pollution has undesirable effects. Ferstandig finds the case unproven.

2.11.2 Short term effects

The short term effects of trace levels of anaesthetic is equally unsure. Bruce and Bach (1976) indicate that concentrations as low as 50 ppm nitrous oxide and 1 ppm halothane could affect performance and summarised their findings "... an anaesthetist who is not at his best, either from fatigue or other causes, knows what to do but might be slow appreciating the situation in which he should do it. The present study does not show that the performance of an anaesthetist is adversely affected by occupational exposure to anaesthetic agents. It only suggests strongly that this could be the case." Both Cohen (1980) and Spence (1980) agree that the issue of performance potential in the pressence of trace anaesthetic gas remains unresolved despite the obvious clinical importance. While Spence is fairly non-commital about the risks pointing out that nobody maintains that occupational exposure to anaesthetic is beneficial Cohen states that he remains "convinced by the validity of the experimental data, the seriousness of the problem and the morality of the issue. In good conscience it is difficult to mount valid arguments against efforts to reduce waste anaesthetic exposure." It is worthy of note that both the UK and US governments have schemes for monitoring the health of women working in operating theatres and the US have guide lines (NOISH 1977) concerning the maximum level of anaesthetic pollution recommended. Ferstandig's paper does not cover short-term effects which may include headaches, lack of concentration and blockage (Gelbicova-Ruzickova, Norak and Janak 1972).

Summarising the effects of waste anaesthetic gases; there is a concensus that implies that exposure to these gases affect the individual, both in the short term and in the long term, though these findings have not been conclusively proven. Further work in this area possibly using dentists for long term studies is indicated.

2.11.3 Minor advantages

There are other advantages, apart from the reduction of pollution,

these are of secondary importance and result from conservation of heat and water vapour. Intubation of the trachea by-passes the normal physiological mechanisms for humidifying inspired gases. So in open and semi-open anaesthesia it may be necessary to humidify the dry fresh-gas supply. However in the closed-loop mode once equilibrium has been established the inspired gas will be fully saturated at or near body temperature. In addition to conserving water vapour the totally closed system will also conserve heat and, since the soda lime carbon dioxide absorber gets hot during use due to its exothermic reaction, the circuit may actively assist in maintaining the patient's temperature. This is probably not of much clinical importance except perhaps in babies and small children. However, active warming of hypothermic patients has been successfully achieved by heating inspired gas.

Thus to summarise the advantages of closed-loop anaesthesia before considering the disadvantages. These are low fresh-gas flow-rate, hence saving expenditure of oxygen, nitrous oxide, and anaesthetic inhalation agent, conserving heat and humidity and reduction of pollution of the theatre which may affect the health of theatre personnel.

2.12 Disadvantages of Closed-Loop Circuits

To be balanced against these advantages are several disadvantages.

2.12.1 Instrumentation Required

The concentration of various gases within the circuit are not immediately apparent. This requires that either an excess of oxygen, to that required by the patient, is given to account for leaks and prevent apoxia, also the patient should be rigorously observed to determine the anaesthetic plane, or alternatively some form of instrumentation is required. Oxygen concentration may be measured either by a paramagnetic oxygen analyser, polarographic meter or by use of a fuel cell. The

concentration of vaporized inhalation agent would also need to be measured. These are the only essential measurements since nitrous oxide is not very potent and carbon dioxide is absorbed. Just these two measurements ensure that the patient gets sufficient oxygen, and not too much potent anaesthetic. Whether there is at present a suitable anaesthetic concentration meter is shown later.

2.12.2 Additional Equipment

Other additional or adapted equipment is needed in closed-loop anaesthesia over those required for open-loop anaesthesia. These include the carbon dioxide absorber, low flow-rate gas-meters and a different type of vaporizer from that used in open-loop anaesthesia. There is no difficulty in changing to a slightly different type of flow-rate meter, and the Goldman vaporizer satisfies the requirement for a relatively inefficient vaporizer to allow very small amounts of anaesthetic-agent to be added to the circuit.

Care must be taken with the soda lime carbon dioxide absorber as the reaction is exothermic and may heat the gas to an unacceptable degree. Care must also be taken that the alkali dust, which may be produced by the reaction, does not get into the air supplied to the patient (White and Halsey 1980). This does not appear to be a serious hazard particularly with modern brands of soda lime canisters that do not get very hot and do not give off appreciable quantities of dust. The canister will require changing from time to time. Some canisters have a visual indication of their state, they change colour as they become used up. Thus little effort is required to note that a canister is nearing the end of its life and replace it.

2.12.3 Minor Disadvantages

An additional difficulty in the closed system is that of maintaining

the fresh-gas supply to balance the circuit and prevent the rebreathing bag from collapsing.

Thus the disadvantages include the necessity of extra equipment above that normally used and the problems of maintaining equilibrium in a closed loop situation.

2.13 Summary of Advantages of Closed-Loop Systems

It has been shown that the only time that an anaesthetic concentration meter would be required is in closed or semi-closed circuit anaesthesia. The advantages of closed-loop systems; low fresh-gas flow-rate, low anaesthetic expenditure, low waste-gas flow-rate with its possible health effects have been discussed together with the disadvantages, unfamiliarity, different equipment required and unknown concentrations. All the expenses are in durables (except for the carbon dioxide absorbers) while the savings are in expendibles. The development of a reliable means of measuring the amount of anaesthetic and oxygen administered would, I believe, tip the balance firmly in favour of the closed-loop system.

2.14 Measurement of Anaesthetic Concentration

There are various ways of measuring the effect of the quantity of anaesthetic being administered. The anaesthetist may closely observe the patient to determine the depth of anaesthesia, or there are automated physiologic meters such as the blood pressure detectors developed independently by Suppan (1977) and Beddard (1965) for instance, or a meter which measures the concentration of anaesthetic that the patient is breathing may be used.

Anaesthetists are used to setting the required concentration on a vaporizer and observing the patient. The use of a meter which gives a direct indication of the concentration of anaesthetic and subsequent adjustment of the vaporizer output coupled with observation of the patient

place similar demands upon the anaesthetist. Adjustments could even be automated so that the anaesthetist would select the required concentration and a feedback loop would maintain it, leaving him as free as before to observe the patient and perform his other duties.

The use of the automated physiologic meters require more attention. This attention may be in the form of fitting a sphygmomanometer cuff, and photoelectric pulse meter (Suppan) or interpretation of the result (Beddard). Both make demands upon the anaesthetist which may be avoided by the use of an anaesthetic concentration meter.

Thus it has been demonstrated that a need exists for a means of determining the effect of the anaesthetic, and a concentration meter of the type described puts the least demands on the anaesthetist.

The following chapters examine available instruments to determine if any are satisfactory for use in closed-loop anaesthesia.

CHAPTER 3

3 Qualities Required of an Anaesthetic Concentration Meter

An anaesthetic concentration meter is used in operating theatres so obviously it should be designed with this environment in mind. It should be constructed so that when properly used there is no danger to the patient, operator or surroundings.

Lamber (1980) states that there is no doubt that monitoring during anaesthesia has contributed to the steady reduction in mortality and morbidity. However, he continues that hazards may arise from instrument malfunction, an inappropriate reliance on data or that the procedures required to interface between the patient and instrument may be dangerous or invasive.

The prime concern of the anaesthetist is that no harm comes to the patient. Thus, care must be taken to ensure that the use of the meter is safe. The nature of the response of the meter to the anaesthetic should be such that the anaethetist can quickly and accurately determine the concentration of anaesthetic present.

The following guide to requirements for a safe anaesthetic-concentration meter is obtained from the "Safety Code for Electro-Medical Apparatus" HMSO (1963), and from observations by the author.

The main requirement for an anaesthetic-concentration meter is that it should be able to measure the concentration of anaesthetic independently of the concentration of the other gases in the anaesthetic circuit. These other gases may include nitrogen, oxygen, nitrous oxide, carbon dioxide and water vapour. The measurement should depend only on the concentration of the anaesthetic, the composition of the other gases should not affect the measurement.

Other points that must be considered when designing such an instrument include: the environment in which it is to work, safety aspects, type of

response required, effect of anaesthetic agents on the materials used and the sample size and contamination of the sample.

3.1 Nature of Response

The meter should respond quickly, though not necessarily swiftly enough to follow breath by breath changes, so a response in 30 seconds should be satisfactory.

A reasonable accuracy is required. For halothane, full scale deflection will probably be about 5%, and the meter should show between 4.9% and 5.1% for this concentration (5% $\pm$ 0.1%). The response should be purely to the anaesthetic measured, that is, there should be no interference from the other anaesthetic circuit gases. Ideally the meter should be sensitive to any of the potent anaesthetic agents allowing universal use.

There should be no zero drift and the need for frequent recalibration should be avoided as both of these would take up the anaesthetist's time and decrease his confidence in the meter. Calibration should be required no more frequently than daily and preferably the meter should require attention at not more than about 3 monthly intervals. Warm up time should be limited to about 5 minutes.

If the meter fails the anaesthetist should be informed and falsely low readings should never be given as this could encourage the anaethetist to increase the concentration, possibly with fatal results. It is desirable that the meter does not rely on a lot of maintenance for satisfactory operation, and it is probably better that the meter should stop working altogether and that this is obvious,than for a falsely low reading to be given.

3.2 Environment

The ambient temperature in the operating theatre is expected to be 20 $^{o}C\pm$ 10 ^{o}C. Blood or other fluids may be spilt on the instrument and it

may be subjected to draughts. Electrical cautery machines produce electrical noise at a frequency of about 0.5 MHz. The meter should work over the range of ambient temperature and be unaffected by spillage, draughs and noise.

There is little unused space around the patient, and it is undesirable to trail leads and tubing around the theatre so the instrument should be small enough to fit the anaesthetic trolley. That is it should be about a 30 cm cube in size.

The only service that the meter may use is mains electricity. To expect the anaesthetist to connect more than that, and a tube for collecting the sample, would be too much. Other services are unlikely to be available anyway.

3.3 Materials

Care should be taken with the selection of materials to be used. Some metals are attacked by anaesthetics. For instance, Appendix B shows the effect of wet halothane on various metals. Rubbers may absorb the anaesthetic; Appendix A shows those affected by halothane. Obviously large quantities of the materials affected should be avoided.

3.4 Safety

The meter needs to be constructed in a workman like manner so that it is sufficiently robust and corrosion resistant to withstand it's normal environment without reduction in safety. The safety aspects may be divided into 3 categories, that is, the meter shall not be dangerous to the patient, operator or surroundings.

Some anaesthetic agents are explosive. The newer agents, however, are generally chosen for their non-inflamability, but if the meter is ever to be used with explosive agents, such as cyclopropane and ether, then it must not produce sparks which could ignite the gas. Naked flames are obviously taboo.

All electrically live parts should be protected to prevent accidental electric shock. It should be impossible to touch live parts, even when interchangeable parts are removed. HMSO (1963) gives details of the electrical characteristics required in terms of insulation and methods of construction.

The meter shall have a leakage current between the mains supply circuit and the patient not exceeding 0.1 mA. So generally the meter should be constructed so that under normal conditions of wear and use it should not be a hazard, and wherever possible if it fails it should do so to an electrically safe state.

3.5 Sample Size and Contamination

If the sample is to be discarded after measurement then it is permissible to contaminate it during measurement. This could occur if the sample is passed through an unsterilised medium, or if ultra-violet light is passed through it. In such cases the sample size should be small, say less than 100 ml/min, to avoid unnecessary waste. If, however, the sample size is large then no contamination of the sample should take place so that it may be returned to the circuit. In this case it may be desirable that parts in contact with the sample are capable of being sterilised.

3.6 Summary of Requirements

The meter should be physically safe, workmanlike in construction and cause no contamination of the anaesthetic circuit. The response, independent of the other gases in the circuit, should be fast (less than 30 seconds) have a reasonable accuracy (for halothane $\pm$0.1% at 5% halothane) and work with a variable ambient temperature (20 ^{o}C $\pm$ 10 ^{o}C). Ideally it should respond to any anaesthetic agent so that it may be used universally. It should conform to the safety code (HMSO 1963).

The following chapter examines meters and transducers that are available to determine if any meet the specification.

CHAPTER 4

4 Anaesthetic Concentration Meters

Anaesthetic meters may be divided into 2 classes. Firstly, there are those that measure a property specific to the anaesthetic, that is, the property is not present in the other anaesthetic circuit gases. This class includes the ultraviolet meter which measures the amount of ultraviolet light absorbed by halothane, and the mass spectrometer which selects a particular mass to charge ratio.

Secondly, there are those meters that measure a property that is not specific. They either rely on the effect of the variable composition being small, compensate for a known composition or use a reference cell. When a reference cell is used it is placed in an anaesthetic-free mixture of the anaesthetic circuit gases and the measurement cell in the inspired mixture. The 2 measurements are compared, the difference is due soley to the anaesthetic. Usually the reference cell is in the fresh gas stream and the sample cell is after the vaporizer. However, an anaesthetic free mixture of the same composition as the anaesthetic-circuit gases is not present in closed circuits, although it may be obtained by filtering.

When using filtering to remove the anaesthetic the comparisons are made before and after the filter. The sonic analyser is an example of a device using filtering.

The meters and transducers discussed below are divided into these categories and a brief description of the principle of operation of the device is given, together with any problems associated with use of the particular device.

4.1 Non-specific devices

The non-specific devices examined here are the adapted katherometer, a semi-conductor device, refractometer, infra-red detector, the

Narkotest, the dielectric constant transducer and the sonic analyser.

4.1.1 Adapted Katherometer

This measures the difference in thermal conductivity between a gas stream with halothane and the same gas stream free of halothane (see Figure 4.1). The gas stream may be, for example, nitrous oxide and oxygen.

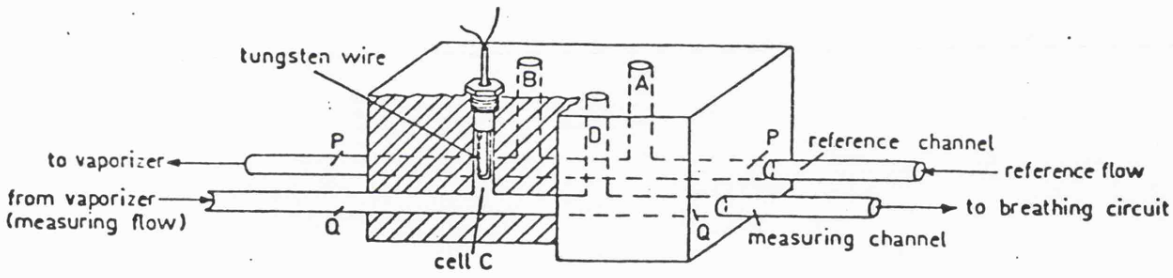


Fig 4.1

Adapted Katherometer showing the Brass Block with the Channels together with one thermistor

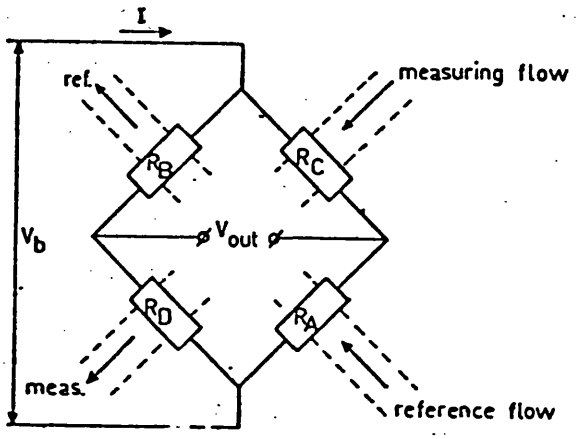


Fig 4.2
Showing the Wheat-stone Bridge arrangement of the Thermistors

The most convenient way to use this transducer is to arrange the 2 thermistors in the halothane free gas to be before the vaporizer, and the 2 in the gas with halothane to be after the vaporizer.

When the vaporizer is off then the same gas flows past all 4 thermistors. The gases will be at the same flow-rate and temperature. The thermistors are all mounted in the same solid brass block, so provided they are matched then there will be no output at Vout (Figure 4.2), as the bridge will be balanced. Turning on the vaporizer, thermistor Rc and Rd will change their resistance and thus cause a change in Vout. Drupsteen, Van Der Hout, Van Der Steen and Massen (1975) show that for a constant current and composition of fresh gas there is a linear relationship between the concentration of halothane and Vout. Concentrations of halothane up to 6% can be determined with an inaccuracy of 0.1%. The 99% response time of the instrument is approximately 1 minute. The thermistors are warm and will cause very slight heating of the gases, but apart from this there is no effect on the gases so the circuit gases may flow past the

thermistors in the circuit. The brass block which the thermistors are mounted in may be attacked by halothane. The response time of this device could be reduced if the thermistors were in the gas stream directly instead of being recessed, although it is likely that if this was done it would make them more sensitive to changes in pressure and flow-rate.

This transducer is satisfactory for measuring the concentration of halothane open loop where a halothane-free mixture of the other gases is available, but it would be unsuitable for the measurement in closed loop where halothane-free mixture is not readily available. The halothane could be filtered out, but problems could arise when the filter became saturated with anaesthetic and should be changed (see next chapter).

4.1.2 Semiconductor Detectors

The paper by Lee and Snowdon (1978) describes measurement of anaesthetic concentrations by the use of the semiconductor which have recently been developed as smoke and pollution monitors.

The gas sensors used are crystalline semiconductors which when heated in the presence of a deoxidising gas or vapour, such as a volatile anaesthetic, absorb cations, and thus increases the number of free electrons and decrease the resistance.

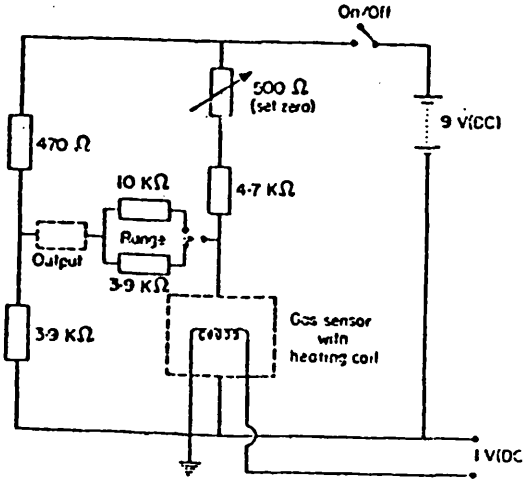


Fig 4.3
The Circuit Diagram for a Gas Detecting Semiconductor

The semiconductor is in a Wheatstone Bridge arrangement as shown in Figure 4.3. The bridge is run from a low voltage 9v dc supply, and the heating coil of the semiconductor from a 1v dc supply. Lee and Snowdon tested diethyl ether, penthrane, chloroform, trilene and halothane. According to the paper satisfactory responses to these were obtained. However, the paper leaves room for doubt as to the suitability of the semiconductor for use in the operating theatre. It says: "A small voltage response was also obtained from other gases likely to be present in clinical anaesthesia", without giving any indication of the size of response. As nitrous oxide may be present in the circuit in concentrations up to 70%, while halothane in concentration about 3%, even if the transducer has a small response per percentage nitrous oxide, it may produce a significant response to 70% nitrous oxide. If "a small response" refers to the concentrations likely to be encountered, then the semiconductor may be satisfactory, but until this point is clarified it has been placed among the non-specific detectors.

The paper also says: "This (the effect of other gases) in practice did not cause any considerable difficulty as the effect could be minimised by adjusting the zero correction", but in closed circuit operation the mixture will not be of constant composition and thus the correction may be impossible.

In their experiments with the semiconductor a couple of explosions occured despite the heater being run at such a low voltage. The explosions happened when high concentrations of ether in oxygen was passed over the detector, but as ether is not commonly used now this should not be a problem.

The response was said to be stable as a nearly constant voltage output was observed for a given concentration on several occasions

over a one year period. The paper does not give any indication of the accuracy of the device, nor does it give many numerical illustrations of the points made. The response time is not given. The response to halothane is comparatively low and non-linear (trichloroethylene 1% to 2% linear 0.25v to 1v, compared with 1% to 2% halothane 0.02v to 0.04v), however, the paper states that preliminary work on some of the more recently introduced gas sensors has shown a more uniform response.

The use of semiconductor detectors in this way is still very much in the experimental stage. Possibly further work could enable them to be useful.

4.1.3 Infra-red Detector

This is a device that works best with a binary mixture or quasi-binary mixture. The infra-red detector makes use of the fact that many gases and vapours absorb specific wavelengths of infra-red radiation. Two beams of infra-red from the same source are produced. One passes through a sealed cell and the other through the sampling cell, falling onto a balanced condenser microphone detector , as shown in Figure 4.4.

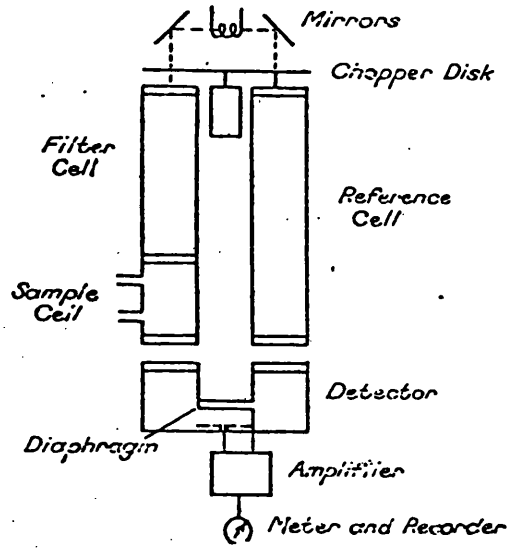


Fig 4.4

The Infra-red

Detector

The sample cell absorbs some of the infra-red making that beam weaker than the sealed cell beam. This means that the detector is warmed more on the sealed cell side, so the flexible diaphram is pushed over from this side. The diaphram forms part of a parallel plate capacitor so the capacitance is altered by the movement. The chopper occludes the infra-red from both cells twice per revolution at an interruption frequency between 6 and 60Hz. As the chopper revolves so the diaphram is caused to move by the changing radiation falling on the detector. The capacitor forms part of the tuning circuit of a radio frequency oscillator. Changes in the sample concentration alter the amplitude of the modulated carrier. This may be demodulated and the signal, which is proportional to the concentration, fed to a meter. The sealed cell is filled with an inert gas such as nitrogen, while the filter cell is filled with a gas whose effect is undesirable. Any of this gas in the sample cell will not affect the absorption as radiation of the wavelength which would be

absorbed by the unrequired gas will already have been absorbed by the filter cell. The detector contains a low partial pressure of the gas to be analysed so that the detector filling can absorb those infra-red wavelengths which are covered by the absorption bands of the substance.

Hill and Stone (1963) describe a particular transistorised infra-red gas analyser which they used to measure a variety of gases: carbon dioxide, nitrous oxide, ether and halothane. During the initial warm-up period a drift equivalent to 0.5% v/v CO_2 occured, after this the drift was 0.1% v/v CO_2 after a further 12 hours. The output deflection (from baseline) for a given CO_2 concentration remained constant within $\pm$1.5% over 20 hours. With a gas sample flow rate of 600 ml/min they were able to follow the CO_2 level in expired air up to 40 breaths per minute, so the response at this high sample flow-rate is rapid. At full scale deflection of 10% v/v CO_2, the analyser warm, the noise at the output was not greater than 0.1% v/v of CO_2. No analysis of the performance with halothane was given.

Hill (1976) states that optical interference filters may be used to select the wave bands appropriate to gases and vapours of interest, though there may be some cross sensitivity in measuring one constituent of a complex mixture with variable concentrations of gases.

4.1.4 Refractometer Instrument

Designed by Diprose and Redman (1978) this meter makes use of the change of refractive index caused by the anaesthetic.

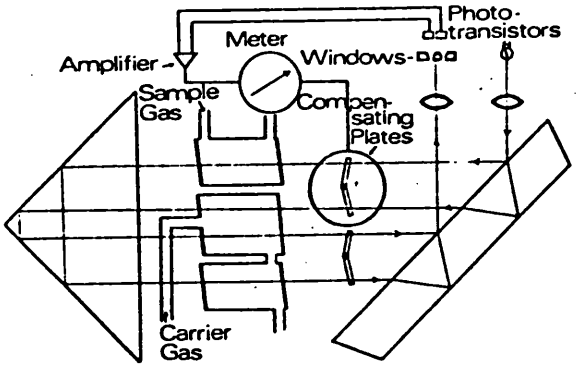


Fig 4.5

An Automatic Interference Refractometer

Light is produced by the lamp and is collumated by the lens. The glass block splits the beam into 2 principle coherent beams. The upper beam passes through the sample gas, while the lower beam passes through the reference gas. The beams are turned through 180° by the prism which is tilted slightly so that when the beams emerge from the glass block they are slightly separate though parallel. The lens causes the beams to pass through its focus. Where these beams cross interference fringes are formed. Changes in the sample gas changes the optical path length and thus the phase of the sample beam and causes movement of the fringes. The movement is compensated for by movement of the compensating plates. The amount of movement required by the plates to keep the fringe pattern stationary is a measure of the concentration of the anaesthetic in the sample.

This meter gives a steady, accurate measurement of the concentration of halothane, or other anaesthetic vapour in air, and is suitable for the measurement of the accuracy of vaporizers, while being a lot less cumbersome than the Rayleigh Refractometer. The meter gives an error of less than $\pm$0.1 vol% in halothane concentration over the range 1-6% halothane. Unfortunately it is sensitive to nitrous oxide and as

such would not be suitable for closed anaesthetic circuit use, where the concentration of nitrous oxide is unknown.

4.1.5 Dielectric Constant Instrument

This transducer described by Gelb and Steen (1970) relies on the properties of the medium (or dielectric) between the parallel plates of a capacitor to affect its capacitance. Capacitance is equal to the dielectric constant of the medium, times the capacitance of the cell in a vacuum. The transducer makes use of 2 capacitors: one which is a reference to act as a thermostat to stabilise the circuit against environmental changes, and to compensate for the particular ratio of the other anaesthetic circuit gases; the other capacitor is the measuring device. A tuned circuit is used to detect the change in capacitance. Details of the circuit were not given in the paper.

This is another device that measures the difference between the gas with anaesthetic, and the same gas composition without the anaesthetic. In the closed circuit this would not be available. Details of the device's accuracy and response time are not given.

4.1.6 Narkotest

This meter uses the swelling caused by absorption of the anaesthetic by silicone rubber to transduce the concentration of anaesthetic.

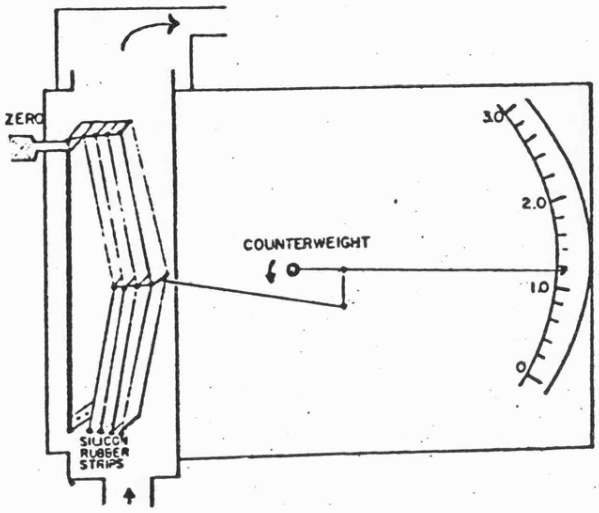


Fig 4.6

A Schematic of the

Narkotest Meter

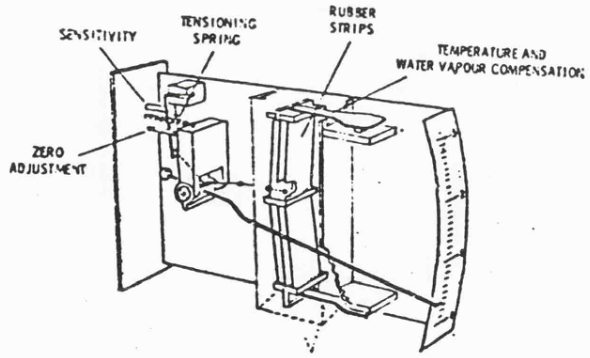


Fig 4.7

Diagram of the

Internal Mechanism

As gases from the anaesthetic circuit pass over the lightly tensioned silicone rubber strips (shown in Figures 4.6 and 4.7), some gases will be absorbed by the strip causing them to swell. This swelling allows the pointer to move in an anticlockwise direction until the tension in the strips is again balanced by the counter weight. The counter weight is acted upon by gravity to produce the balancing

force, so it is important that the meter is mounted and calibrated in a vertical position. White and Wardley-Smith (1972) tested the meter for halothane, cyclopropane, diethyl ether, chloroform, penthrane, ethrane, trilene and divinyl ether and found the meter gave satisfactory results. However, there are several problems with it. It needs to be zeroed frequently. It has a very slow response at low flow rates and even at 4 L/min a 1% halothane reading is only reached after 90 seconds. At high flow rates the meter suffers from flutter. Leaving the meter unused for about 6 hours makes it very sluggish to respond, and it tends to read low. Following the first deflection after being left it is necessary to rezero. So the nature of the response is not particularly satisfactory, as the anaesthetist is at his busiest, and the concentration of halothane most critical at the induction stage when this meter cannot be relied upon for the first operation of the day.

The meter does incorporate compensation for the effects of water vapour and temperature, but other gases affect the readings. A deflection of 0.25 dial units was produced by 100% carbon dioxide, but no deflection could be seen for physiological concentrations. It responds to 100% nitrous oxide with a 0.3 deflection (Lowe and Hagler, 1971).

The meter was found by White and Wardley-Smith (1972) to be accurate within $\pm$0.1% halothane at full scale deflection (3%), provided it had been recently exposed to the agent and rezeroed after a suitable wash out with air, that is, until the pointer ceased to move.

This method of transducing does not cause any changes in the anaesthetic circuit gases and the meter has an extremely low resistance to gas flow through it (0.1cm H_2O at 20 L/min), so it could be connected directly into the respiratory circuit.

Thus the Narkotest meter may be used to detect any of the inhalation anaesthetic agents, but it requires frequent rezeroing, particularly when having been left unused, and it has a slow response time.

4.1.7 Sonic Analyser

The difference in the speed of sound in the heavy hydrocarbon laden vapour from the anaesthetic circuit and the vehicle gases from which the anaesthetic has been removed, provides the means by which this instrument measures the concentration of anaesthetic agent. The analyser described by Molyneux and Pask (1959) is comprised of 3 glass tubes, each a metre long; at one end of each tube there is a sound source, and at the other a receiver. The tubes are connected in series with activated charcoal containers between them, as shown in Figure 4.8.

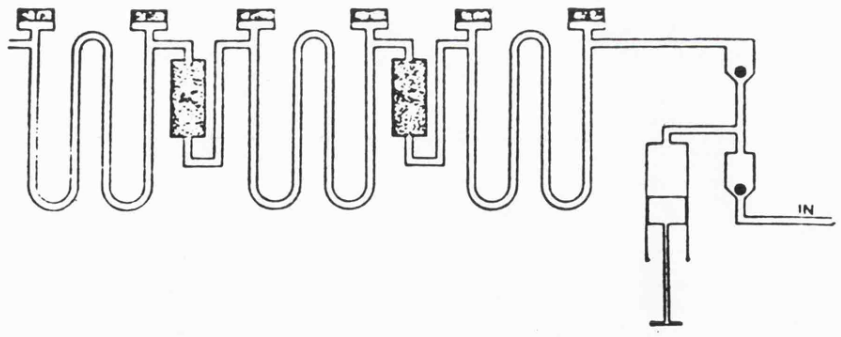


Fig 4.8

Sonic Analyser

The purpose of the activated charcoal is to remove the heavy hydrocarbons so that the change in the delay between sending and receiving the pulses through the anaesthetic-free gases after the first charcoal tube can be measured. The difference in delays should be the same when the first and second tubes are used as it is when the first and

third tubes are used. Variation indicates that the first charcoal canister is saturated.

The calibration of the device is fairly complicated and a different setting up routine is necessary if the vehicle gas contains between 50% and 75% nitrous oxide, than when only oxygen and nitrogen are used. The instrument takes 10 minutes to warm up, even though it is transistorised. Molyneux and Pask testing it at 4% halothane found a mean reading of 3.77% v/v, with a standard deviation of 0.07 over 5 readings. The response time of the instrument is not given. Care must be taken to ensure that the first charcoal canister is replaced immediately it has reached saturation, as falsely low readings will otherwise result.

Thus this instrument is not wholly satisfactory although it will give a response to all anaesthetic agents.

4.3 Specific Detectors

The ones examined here are the mass spectrometer, ultraviolet absorption meter and absorption of anaesthetic by a coated quartz crystal.

4.3.1 Mass Spectrometer

Ions of uniform velocity entering a uniform magnetic field are caused to travel a circular path, the radius of which depends on the mass to charge ratio of the ion. The mass srectrometer uses this principle.

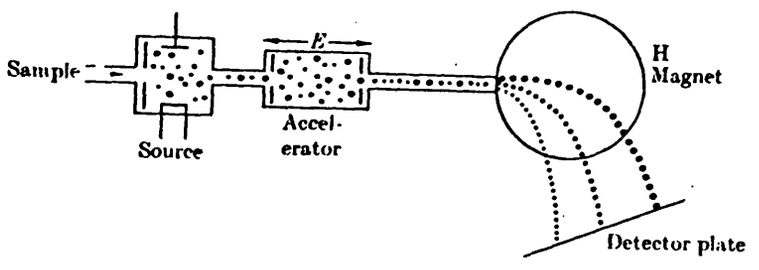


Fig 4.9
A Mass Spectrometer (From Strobel 1973)

Considering Figure 4.9 the sample, at low pressure, enters the first chamber where it is ionised. It then passes into the acceleration chamber where it is subject to a uniform electrostatic field. It then passes into the separation chamber where it experiences a uniform magnetic field. Ions of large mass to charge ratio will be least deflected, that is, they will have a large radius of curvature. So depending on the mass to charge ratio the ions will travel different paths. The separated ions then fall on the detector and measurement of their concentration can be made. By placing the detector where the principle ion of halothane falls, it can be selected.

This is the usual type of mass spectrometer although there are others. The quadrupole mass spectrometer is useful when a particular ion is required.

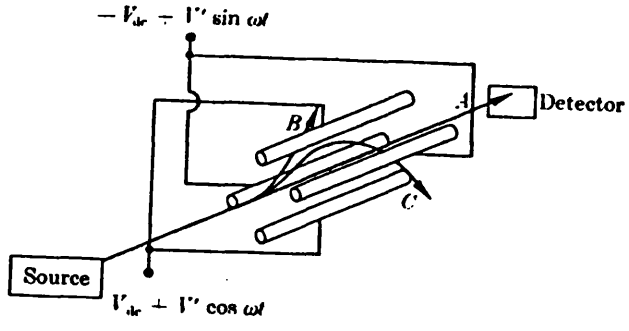


Fig 4.10
Quadrupole Mass Spectrometer

The quadrupole mass spectrometer shown in Figure 4.10 consists of 4 parellel rods that sort the ions length ways as they pass between the rods. One diagonally oprosite pair of rods is held at +Vdc volts, with the other pair at -Vdc volts. A radio frequency signal is superimposed on one pair and the same signal shifted through 180° (that is out of phase) is superimposed on the other pair. Only ions

of a particular mass to charge ratio will pass through the field for a particular setting of the dc voltage and radio frequency signal. By setting these the principal halothane ion may be selected and concentration measurement made. Any particular anaesthetic could be selected for measurement.

This device is suitable for research, and though generally expensive, a relatively cheap version was designed by Smith and Cromey (1968). But the instrument still suffers from the need to have a very low pressure of inlet gas, of the order of 10^{-6} millibar. This requires a reasonable quality vacuum pump. Modern research spectrometers carry out analysis on gas samples as small as 10^{-8}cc at STP. The detection sensitivity is about 10^{3} molecules/cc, which corresponds to a pressure of 10^{-16} atm (Melton 1970). Thus to use a mass spectrometer for routine measurement of anaesthetic concentration would be extremely extravagent.

4.3.2 Absorption of Ultraviolet

Halothane strongly absorbs ultraviolet, the maximum absorption being in the region of 200 nano-metres. Unfortunately there is no convenient source of this wavelength, but halothane still absorbs adequately at the 234 nano-metre emission of low pressure mercury lamps.

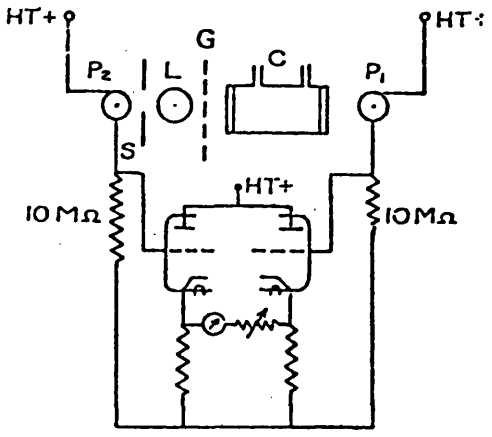


Fig 4.11
The Ultraviolet Meter
(From Scurr and Feldman, 1974)

The 2 photocells P1 and P2 in Figure 4.11 are situated so that one receives the light directly from the lamp L, and the other receives the light after it has passed through the sample cell C. Both the envelopes of the photocells and the windows of the sample cell are made from quartz, as ordinary glass absorbs ultraviolet. The current from the photocells is proportional to the amount of ultraviolet falling on them. These currents produce voltages which are supplied to the operational amplifier which amplifies the difference. A meter indicates the measured concentration. Robinson, Denson and Summers (1962) say the device needs 15 minutes warm-up time, and that drift after this is negligible. However, from observation of the meter, it suffers from substantial drift which may be erratic and cause sweeps across the whole scale. The response is linear with concentration of halothane. A 15cc cell volume was used with a sample gas flow rate of 100cc/min. A complete response was achieved in 20 seconds; the accuracy of the meter was not stated.

The action of ultraviolet light on halothane gives rise to parts per million of irritant decomposition products. For this reason it is better not to feed the sample back into the circuit.

The main problem with this instrument is the drift and instability which is attributable to the lamp. Movement of plasma within the envelope results in unequal intensities of light falling on the 2 photocells. That is, the light falling on a particular photocell varies as the plasma moves, and the ratio of the light intensities falling on the photocells is not constant. This causes unpredictable variation in the output.

An adapted design by Diprose, Epstein and Redman (1980) has greatly improved this instrument. The improvement was obtained by rearranging the original photocells and lamp, and adding a beam splitter so that the 2 photocells are "looking" at the same light. Further improvement was achieved by use of a hot cathode lamp with which the cells could be placed side by side, as the light was sufficiently constant through the beam width. The device was found to be accurate to 0.05% with zero drift of less than 0.25% halothane over 15 hr after a 5 min warm-up period. The inherent response time was about 2 seconds, although in practice the dominant delay is likely to be due to drawing the sample through the connecting tube. For example the transit time for a 2mm bore tube at a sampling flow rate of 50ml/min would be 4 sec/metre length.

The improved version of the ultraviolet halothane instrument is suitable for work in the operating theatre. However, it is only useful for measurement of halothane.

4.3.3 Quartz Crystal Transducer

Quartz crystals have been used for a long time as pressure and acceleration transducers. When the crystal is in a resonator circuit it will oscillate at a very stable frequency. This frequency is largely determined by the thickness of the crystal and mass which is made up of the mass of the crystal, the electrodes and any other mass

acting on the crystal's surface. Additional mass will cause a frequency change which can be detected by comparing the frequency of the test crystal with the frequency of a reference and undisturbed crystal.

In this application described by Gedeon, Hamilton, Kindlund and Lundstrom (1980), the crystal is coated with a silicone oil which absorbs, or adsorbs, the anaesthetic. The amount absorbed, and hence the frequency change, is proportional to the concentration of anaesthetic. Nitrous oxide, oxygen, carbon dioxide and nitrogen are not absorbed, and so do not interfere with the frequency. Water vapour at 100% humidity, 25 ^{o}C, produces a change equivalent to 0.15% halothane.

The device is reported to be extremely stable, with a long term stability of 0.1%. The inherent response time is 0.1sec. Engstrom developed the monitor, called the Emma, as a multigas monitor for anaesthesia (ie Engstrom's Multigas Monitor for Anaesthesia) and it can detect halothane, enflurane, methoxyflurane and isoflurane with a typical sensitivity of 0.02%.

This device is new and at present undergoing trials in this country. If all the makers' claims are substantiated, then the monitor will meet all the requirements.

4.4 Review

Many of the devices examined compare a particular property of the anaesthetic-free gas and the gas with anaesthetic. This is a valid method where these gases are available, however, this is not the case in closed loop systems.

The only instruments that are not sensitive to both the anaesthetic and the composition of the other gases are the mass spectrometer, the Emma and the ultraviolet meter. The improved ultraviolet meter is

sensitive to halothane only and the mass spectrometer extravagant unless several theatres share the same unit.

Thus the only satisfactory instrument available, the Emma, is unproven.

CHAPTER 5

5 The Search for a Means of Measurement

The problem of measurement is to be able to measure the concentration of any anaesthetic agent against a background of the other anaesthetic circuit gases. The main constituent gases in an anaesthetic circuit are known but their relative concentrations are not. Let us examine the gases and propose a criterion by which a measurement solution would be considered satisfactory.

Various methods of measurement may then be examined.

5.1 Anaesthetic Circuit Gases

The main gases in a closed anaesthetic circuit are nitrous oxide, oxygen, nitrogen, carbon dioxide, water vapour and the potent anaesthetic agent. These gases constitute most of the circuit gases, but others include the noble gases from the air in the lungs before anaesthesia commences and numerous organic compounds. Krotoszynski, Gabriel and O'Neill (1977) characterised human expired air and found 102 organic compounds in the breath of a 25 year old healthy Caucasian male. 97% of the compounds fall within the trace level range of 0.06 to 9.5 nanograms per litre. These are unlikely to be in great enough concentration to cause a significant measurement problem.

The most commonly used anaesthetic in Britain is halothane but other agents may be used including enflurane, ether and chloroform. The latter 2 are not generally used in developed countries, but are used in the third world where the newer safe agents are too expensive.

The anaesthetic circuit gases are described below and their approximate concentrations given.

5.1.1 Oxygen

Formula O_2. Molecular weight 32. Approximate concentration in circuit 30-40%. Source - fresh gas supply. Purpose - to sustain life.

Oxygen in air is present in 20.9% and is necessary to sustain life. A higher percentage is required during anaesthesia as the unconscious patient does not utilise it as efficiently.

Care must be taken, particularly in fully closed circuits, to replenish the oxygen removed from the circuit by respiration.

5.1.2 Nitrogen

Formula N_2. Molecular weight 28. Source - wash out from patient.

Inhaled nitrogen dissolves slightly in the blood and other body fluids; a small amount of this dissolved nitrogen will wash out of the patient during the course of an operation.

The concentration of nitrogen in the patient's lungs (aveoli) before anaesthesia is 74.1%. (The rest being 14.5% oxygen, 5.3% carbon dioxide and 6.1% water vapour.) In the circuit the concentration will be significantly less than this as the expired gas is mixed with the large volume of the anaesthetic circuit. Nitrogen will be lost from the circuit, either with the waste gases in the open circuits, or in the closed circuits by sampling and leaks, so the concentration will decrease as the operation progresses.

5.1.3 Nitrous Oxide

Formula N_2O. Molecular weight 44. Approximate concentration in circuit - 50-80%[1]. Source - fresh gas supply. Purpose - to provide some anaesthetic effect.

This gas is used as a filler as it has some anaesthetic effect. When used as the sole anaesthetic agent at atmospheric pressure it will not put the patient into the third stage of anaesthesia. Nitrous oxide has a Mac (minimum aveolar concentration of anaesthetic required to prevent gross movement in response to standard stimulus in the dog) value of

[1] Atkinson, Rushman and Lee (1977)

105 vol%, compared with 0.75 vol% for halothane.

It is the only inorganic compound used as an anaesthetic. It is non inflamable under normal operating conditions.

5.1.4 Carbon Dioxide

Formula CO_2. Molecular weight 44. Concentration varies through the circuit up to 5%. Source - exhaled by patient.

This must be removed from the closed circuit as prolonged exposure to concentrations in excess of 5% carbon dioxide may produce unconsciousness and death. The carbon dioxide is removed by soda lime canisters, so there will not be a constant concentration of this throughout the circuit.

5.5.5 Water Vapour

Formula H_2O. Molecular weight 18. Concentration - saturated at temperature of circuit. Source - exhaled by patient.

The patient exhales air saturated with water vapour at body temperature (37 ^{o}C). The circuit gases will be slightly below this temperature, so water is expected to condense in the circuit and may require removal.

5.1.6 Important Anaesthetic Agents

Before considering individual anaesthetic agents let us look at the broad requirements for anaesthetic agents which were drawn up by Raventos and Spinks (1958). They wrote guide lines to define a way of determining the suitability of an agent for clinical use.

Starting with the effects on the patient; the agent should have a high potency, rapid and quiet induction and recovery and freedom from severe cardiovascular effects. It should have a high therapeutic index, that is the ratio of its anaesthetic and lethal concentrations

which defines the gross safety margin.

These points do not give much insight into the nature of the compounds, the only guidelines on the chemical and physical properties are that the agents are required to have a low boiling point (that is below 60-70 °C), and be non-inflamable. The low boiling point limits the size of the molecule and ensures easy vaporization. Non-inflammability is achieved by making use of halogens in the compounds, particularly fluorine which reduces chemical activity (Sucking (1958)).

Any anaesthetic agents developed in the future are likely to follow these guidelines. So if a common parameter is sought in order that one meter may measure any anaesthetic then a transducer which detects the presence of the halogens, or the higher (though limited) molecular weight of the anaesthetic agents compared with the other anaesthetic circuit gases, may be used.

Considered below are some of the anaesthetic agents which are used now or have been used in the past. All the anaesthetics except cyclopropane are liquid at normal temperature and pressure, and are vaporized by having the vehicle gas passed through them. They are also all halogenated hydrocarbons of reasonably low molecular weight. Cyclopropane is a gaseous hydrocarbon.

5.1.6.1 2-Bromo-2-Chloro-1, 1, 1 Trifluoroethane. (Halothane or Fluothane)

Formula $CF_3CHBrCl$. Molecular weight 197. Vapour concentration for anaesthesia - 0.5-2.0% ①.

This is the most commonly used anaesthetic agent in Britain.

5.1.6.2 Enflurane (Ethrane)

Formula CF_2HOCF_2CHFCl. Molecular weight 184.5. Vapour concentration for anaesthesia - 1.5-3.0% ①.

This is another of the newer non-inflammable agents.

5.1.6.3 Cyclopropane

Formula C_3H_6. Molecular weight 42. Gas concentration for anaesthesia - 5-20%[1]. Supplied from medical gas cylinders.

This is a flammable anaesthetic which is rarely used owing to its expense and the danger of explosion. When it is used it is generally in closed circuits.

5.1.6.4 Chloroform

Formula $CHCl_3$. Molecular weight 119. Vapour concentration for anaesthesia - 0.5-2.0%[1].

This agent combines high potency with a narrow safety margin. It is non-inflammable. It is not generally used in developed countries.

5.1.6.5 Trichloroethylene (Trilene)

Formula C_2HCl_3. Molecular weight 131. Vapour concentration for anaesthesia - 0.2-2%[1].

This agent cannot be used in a closed circuit when a soda lime carbon dioxide absorber is used. This is because contact with the soda lime which is hot, due to the exothermic reaction which occurs when the carbon dioxide is absorbed, causes dichloroacetylene to be formed which is both neurotoxic and explosive.

5.2 Summary of Gaseous Concentration in Closed Circuits

Considering a closed circuit using nitrous oxide with halothane as the principal anaesthetic agent. There will be approximately 0.5-2% halothane, 50-70% nitrous oxide and 30-50% oxygen. Carbon dioxide will be removed by passing the gases through soda lime and the gases will be saturated with water vapour. There will be a small concentration of nitrogen, together with trace concentrations of numerous other gases.

Thus the measurement of halothane is to be made against a background of a variable concentration of principally nitrous oxide and oxygen, small concentrations of nitrogen, water vapour and carbon dioxide and extremely small concentrations of numerous other organic compounds and air constituents.

5.3 Criterion for Acceptance of a Measurement Method

Obviously we want to be able to measure the concentration of any anaesthetic agent against the background discussed, without appreciable effect on the measurement by the composition of the other gases. An accuracy in the region of 1/4% of the total gas volume is sought.

This is the most important consideration and will be referred to as the criterion. Thus the criterion is that the expected range of concentrations of the other gases should produce an effect equal to, or less than, a $\pm$0.1% change in the concentration of the anaesthetic measured.

If a property existed such that all the other anaesthetic circuit gases had the same value of this property, and the anaesthetic agents had a significantly different value, then this would be an ideal solution. The composition of the other gases would be immaterial. No such property was found nor was a property found that would be satisfactory by the criterion.

The measurement method chosen will have to determine the concentration quickly (it should complete the measurement in less than 30 seconds)and be safe for use in the operating theatre.

Chemical methods will probably be too slow, so to determine if there is a way to measure the concentration which is acceptable, physical methods of measurement were examined.

5.4 Physical Methods of Measurement

Various physical methods were examined but none were found to be entirely satisfactory on the grounds of interference with the measurement by the other constituent gases. That is by the criterion of 5.3.

When insufficient data was available for the newer inhalation agents, it was decided to investigate to see if a suitable property could be found for chloroform, for which data is generally given. If a satisfactory quality was found for chloroform, an experimental rig could be made to determine if the newer inhalation agents responded similarly.

5.4.1 Refractivity = (1 - Refracture index) x 10^6

H_2O 254 ③ O_2 272 ③ N_2 297 ③

CO_2 451 ③ N_2O 516 ③

Halothane 1510 ④ Chloroform 1450 ③

The denser anaesthetic vapours have a higher refractive index than the other anaesthetic circuit gases, though this is not sufficiently great to be of use by the criterion of 5.3.

5.4.2 Dielectric Constant

O_2 1 0005 ⑤ N_2 1 0005 ⑤

CO_2 1 0009 ⑤ N_2O 1 0011 ⑤

Halothane 1 008 ⑤ Trilene 1 008 ⑤

The dielectric constant is proportional to the refractive index squared for non-absorbing gases at radio frequencies. Again there is not a sufficiently great difference for this property to be used.

② Washburn (1929)

③ Kaye and Laby (1975)

④ Scurr and Feldman (1974)

⑤ Gelb and Steen (1970)

5.4.3 Ultra-Violet Absorption

Start of UV absorption.

O_2, N_2, CO_2, H_2O - no absorption

N_2O 225 nm [6] halothane 270 nm [6]

Chloroform 235 nm [6] trilene 262 nm [6]

Only halothane and trilene absorb light from the convenient source of a low vapour mercury lamp at 254 nanometers, so although there will be no interferance from the other anaesthetic circuit gases, the measurement of the absorption is only suitable for these 2 vapours.

5.4.4 Velocity of Sound

CO_2 259_{Δ} m/sec [3] N_2O $268_{\square}$ m/sec [3]

O_2 332_{*} m/sec [3] N_2 337_{Δ} m/sec [3]

H_2O 405_{o} m/sec [3]

Chloroform $155_{\square}$ m/sec [3]

Δ at 0 °C $\square$ at 20 °C $*$ at 31 °C $_{o}$ at 100 °C

The velocity of sound is inversely proportionally to the square root of the molecular weight, and not sufficiently different by the criterion of 5.3.

5.4.5 Viscosity

CO_2 14.7 Nsm^{-2} [3] N_2 17.6 Nsm^{-2} [3]

N_2O 14.6 Nsm^{-2} [3] O_2 20.4 Msm^{-2} [3]

Chloroform 10.2 Nsm^{-2} [3]

Viscosity is proportional to the square root of the molecular weight and again there is insufficient difference.

[6] Robinson, Denson and Summers (1962)

5.4.6 Thermal Conductivity

CO_2 1.37_{Δ} [2] N_2O 1.44_{Δ} [2] H_2O 2.17_{o} [2]

N_2 2.28_{Δ} [2] O_2 2.33_{Δ} [2]

Chloroform 0.608_{Δ} [2]

Δ = 0 °C o = 100 °C

(All in joules/sec/cm^3 x 10^4/ °C)

A change in the relative concentrations of carbon dioxide or oxygen of the order of a few percent would have the same effect as the range of chloroform concentrations. So by the criterion of 5.3 this will not be satisfactory.

As no physical parameter was found it was decided to search for other methods of determining the concentration of anaesthetic.

The anaesthetic could not be satisfactorily determined in the mixture, but if the mixture could be separated out into its component gases, then any transducer that measures some quality of the anaesthetic could be used.

5.5 Separation of Gases

There are several methods of separation of gases. In this case it is important that the separation is fast, of the order of seconds, and that the operation is fail safe. It will not be essential that each component is separated from each of the others, but the potent anaesthetic should be separate from the other anaesthetic circuit gases.

Basically separating methods may be divided into 2 approaches. In one a particular gas is filtered out, that is it is prevented from passing through the material. The other method separates by different constituents following different paths.

5.5.1 Filtering

In this method the substance filtered out is retained on the filtering material. Activated charcoal is one such material.

Activated charcoal is a porous substance which will take up many gases in different amounts. The more condensible gases are absorbed in greater quantities. Molecules which can more readily slow down to the comparative rest state should, by the same token, be more easily captured by a solid surface. Thus the anaesthetic agents will be absorbed by the activated carbon and retained by it until the carbon is saturated with anaesthetic. When saturated, anaesthetic would pass through the filter. The carbon may be reactivated by heating it to drive off compounds retained.

Extreme care would be needed to ensure that before the carbon becomes saturated with anaesthetic, the carbon is changed or reactivated . There must be some means of determining the state of the carbon. This may be done by using 2 canisters of the filter. The measurement is done on the gas between the 2 canisters, and after the second canister. Differences in these measurements would indicate that the first canister had not absorbed all of the anaesthetic and so should be changed.

It will be inconvenient to have to rely on changing parts of the instrument to ensure satisfactory operation. This method is, therefore, to be avoided if possible.

5.5.2 Variable Path Separators

The mass spectometer separates by causing different ions to travel different paths in a magnetic field. As previously stated, this is an expensive and large piece of equipment, and thus not suitable for routine theatre use. The cost may be justified if the mass spectrometer can be multiplexed between a number of theatres in a complex,

though this may be at the expense of speed, as samples may have to be pumped through pipes tens of metres long.

Molecular sieves and gas chromatography are other methods that separate gases.

5.5.2.1 Molecular Sieves

A molecular sieve is a porous solid which separates out particles by molecular dimension. They are usually zeolites which are hydrated metal aluminosilicate compounds with well defined crystalline structures. Upon heating, the zeolites lose their water content with little or no change in their crystal structure, so pores of closely controlled size that act as sieves are generated.

Molecular sieves may be used in molecular sieve chromatography. Large molecules cannot pass through the pores and travel down the column by the shortest route possible emerging quickly. Smaller molecules can pass through the pores and gain access to the internal volumes; they therefore perculate down through the column by a longer path length and emerge more slowly.

Although this would probably give the fast separation required, water molecules are readily absorbed and retained by molecular sieves so, as water vapour will be present in the sample, the pores in the zeolite will become filled and the efficiency of the column as a separator would reduce. Again the zeolite may be reactivated by heating, but as with activated carbon, this is to be avoided if possible.

5.5.2.2 Gas Chromatography

In gas chromatography a small sample of the gas to be analysed is introduced into an inert carrier gas stream which passes through the column. The column is an inert, solid support of large surface area, coated with a non-volatile liquid and packed into a glass or stainless steel tube.

The sample will dissolve in the liquid at the head of the column, evaporate, and redissolve further down the column. This process continues through the column until the sample eventually emerges. Differences in the solubilities of different component of a mixture result in different molecules spending different lengths of time in the column, and so emerge at different times.

By its nature gas chromatography is not a continuous method of measurement; a small sample is allowed to pass through the column before the next sample is introduced. For operating theatre use it is necessary that it separates as quickly as possible to accurately reflect the current gas composition. A satisfactory separation should be achieved, at most in 30 seconds, and preferably less.

5.6 Review of Methods of Measurement

No satisfactory physical method, not using separation, was found which would give the concentration of anaesthetic against the background of a variable composition of the other circuit gases. Methods of separating the gases were explored. The use of activated carbon and molecular sieves were considered unsatisfactory owing to retention of compounds causing limited life between reactivations. Gas chromatography which does not retain compounds permanently was considered worthy of further study.

CHAPTER 6

6 Gas Chromatograph

This consists essentially of a tube (the column) packed with inert granules that have been coated with a non-volatile liquid (the stationary, or liquid phase). An inert carrier gas (the mobile phase) passes continuously through the column, and samples of the gas to be separated are introduced periodically into the carrier-gas stream by a gas sampling valve. The gases emerging from the column (the elutant) pass through a detector, which senses a difference between the sample gases and the carrier gas. The response will be a series of peaks as each compenent of the sample passes through the detector.

A gas chromatograph is represented in block diagram form in figure 6.1.

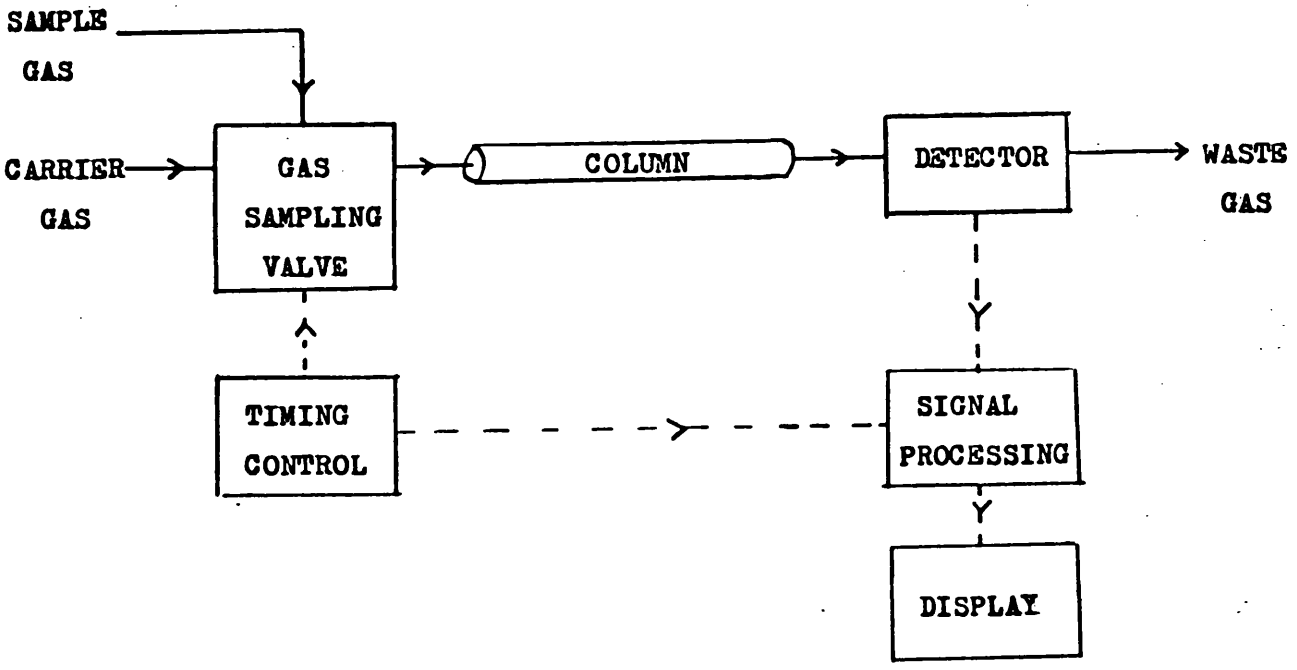


Figure 6.1

Before considering the practical aspects of gas chromatography let us examine what happens in the column. It is in the column that the separation takes place.

6.1 Theory of the Separation by the Column

As the sample enters the column some will dissolve in the liquid phase, and then evaporate only to re-dissolve further down the column. Dissolving is encouraged by the liquid phase having a large surface area as it is coated on fine particles. The dissolving and evaporating continues until the sample emerges from the column.

Components of a mixture are separated if their solubility in the liquid phase is different, and the column is long enough to allow them to separate. Although the processes that take place in the column are continuous, it is convenient to build up a discontinuous model as a first approximation.

6.1.1 Discontinuous Model of Column

Initially we will be concerned with just one component of the sample gas. The column is considered to be made up of a number of connected volumes called plates. The total volume of a plate is made up of the gas volume and the liquid volume; the volume occupied by the solid support is ignored.

At equilibrium there will be a certain fraction of sample in the gas phase. Let this be $\bar{x}$, and the fraction in the liquid phase be y.

$$\bar{x} = 1-y$$

A partition coefficient (K) is defined as the ratio of the concentration in the liquid phase to the concentration in the gas phase.

That is $K = \bar{x}/y$ 1

By making the following assumptions, a discontinuous model of chromatography may be developed. The assumptions are:

1 The partition coefficient is constant throughout the column, and is independent of concentration.

2 Equilibrium of the solute between phases is rapid compared with the rate of travel of the mobile phase.

3 Diffusion along the length of the column in any phase is negligible.

4 The column can be considered to consist of a number of identical volume elements, in each of which one equilibrium occurs.

5 The flow of mobile phase can be regarded as discontinuous, that is, it consists of a stepwise addition of volumes of mobile phase, each equal to the free volume per plate.

The sample of volume m enters the first plate and is contained within the plate. It reaches equilibrium, $\frac{1}{K}$m in the gas phase and ym in the liquid phase. The next volume of carrier gas is added and the sample in the mobile phase is swept onto the next plate where equilibium is again established. The total sample in the second plate will be $\frac{1}{K}$ x m, $\frac{1}{K}$ x $\frac{1}{K}$ x m in the gas phase and $\frac{1}{K}$ x y x m in the liquid phase. In the first plate some of the sample in the liquid phase will evaporate into the gas phase. The total volume in the first plate at this instant will be y x m, y x $\frac{1}{K}$ x m in the gas phase, y x y x m in the liquid phase. At each additon of carrier gas the sample in the mobile phase is carried over to the next plate and equilibrium is re-established.

This is shown in Figure 6.2 where m = 1 for simplicity.

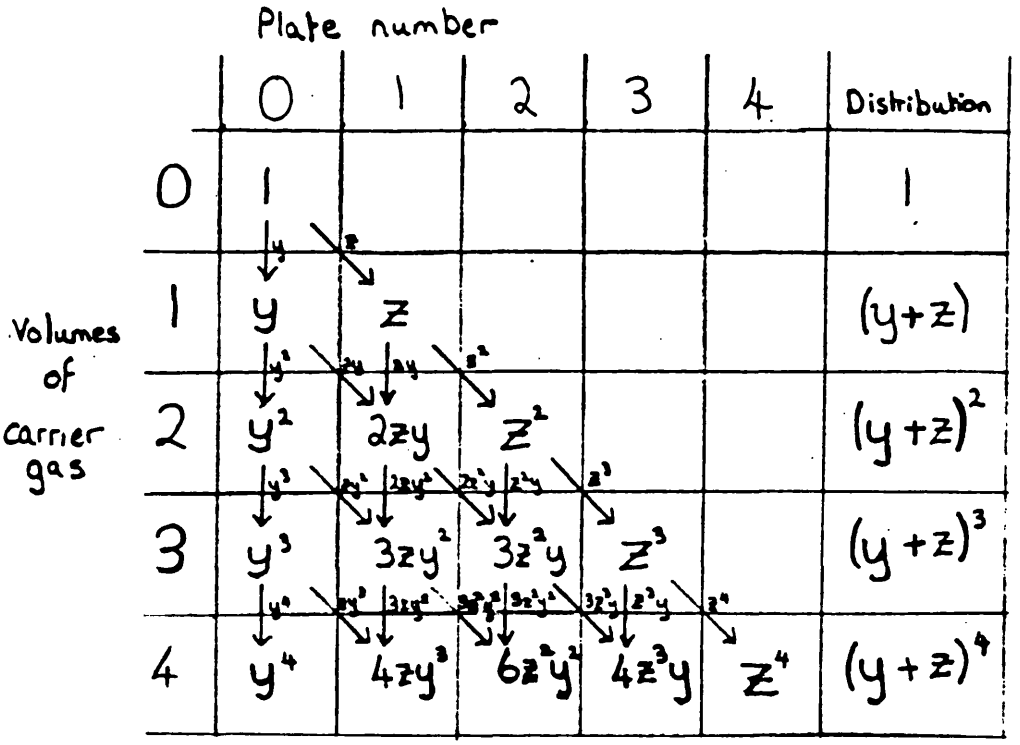


Figure 6.2

The sample is divided between the liquid phase and the gas phase y of the total plate volume in the liquid, x of it in the gas phase. Clearly in each plate the quantity of solute corresponds to a term in the binomial expansion. So if r volumes of carrier gas have been added to the column the distribution can be represented by the expansion of $(x + y)^r$. Designating the number of any plate as N, the value of any term in the expansion is given by

$$Q_{N+1} = \frac{r!\, y^{(r-N)}\, z^N}{N!\,(r-N)!} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 2$$

If we are concerned with a column of length N and are interested in the amount eluting (Q_E), then clearly the elutant will be the fraction in the gas phase which has come from the Nth plate as shown in Figure 6.3.

Volumes of carrier gas	Plate Number 0	1	2	3	4	Elution
4	y^4	$4zy^3$	$6z^2y^2$	$4z^3y$	z^4	
5	y^5	$5zy^4$	$10z^2y^3$	$10z^3y^2$	$5z^4y$	z^5
6	y^6	$6zy^5$	$15z^2y^4$	$20z^3y^3$	$15z^4y^2$	$5z^5y$
7	y^7	$7zy^6$	$21z^2y^5$	$35z^3y^4$	$35z^4y^3$	$15z^5y^2$
8	y^8	$8zy^7$	$28z^2y^6$	$56z^3y^5$	$70z^4y^4$	$35z^5y^3$

Figure 6.3

$$Q_E = \frac{(r-1)!\ y^{(r-1-N)}\ z^{(N+1)}}{N!\ (r-1-N)!} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ 3$$

Let us propose that the number of gas volumes which must be added to the column before the peak (Qmax) is eluted is R.

$$Qmax = \frac{(R-1)!\ y^{(R-1-N)}\ \bar{z}^{N+1}}{N!\ (R-1-N)!} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ 4$$

It follows that the quantity of sample eluting at time R - 1 and R + 1 is less than Qmax.

For R + 1:

$$\frac{R!\ y^{R-N}\ \bar{z}^{N+1}}{N!\ (R-N)!} < \frac{(R-1)!\ y^{(R-1-N)}\ \bar{z}^{N+1}}{N!\ (R-1-N)!} \quad \ldots 5$$

R, N, $\bar{z}$ and y are all positive quantities as is (R - 1 - N).

from 5
$$\frac{R\ y}{R-N} < 1 \quad \ldots\ldots\ldots\ldots\ldots\ 6$$

For R - 1:

$$\frac{(R-2)!\ y^{(R-2-N)}\ \bar{z}^{N+1}}{N!\ (R-2-N)!} < \frac{(R-1)!\ y^{(R-1-N)}\ \bar{z}^{N+1}}{N!\ (R-1-N)!} \quad \ldots 7$$

$$1 < \frac{(R-1)\ y}{R-1-N} \quad \ldots\ldots\ldots\ldots\ldots\ 8$$

Substituting $y = 1 - \bar{z}$ in 6 and 8.

$$R - R\bar{z} < R - N \quad \ldots\ldots\ldots\ldots\ 9$$

$$R\bar{z} > N \quad \ldots\ldots\ldots\ldots\ 10$$

and
$$R - 1 - N < (R-1)(1-\bar{z}) \quad \ldots\ldots\ldots\ldots\ 11$$

$$R - 1 - N < R - 1 - R\bar{z} - \bar{z} \quad \ldots\ldots\ldots\ldots\ 12$$

$$-N < -(R+1)\bar{z} \quad \ldots\ldots\ldots\ldots\ 13$$

$$N > (R+1)\bar{z} \quad \ldots\ldots\ldots\ldots\ 14$$

Since $\not{Z}$ is fractional, for all intents and purposes the peak emerges when

$$R = \frac{N}{\not{Z}} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots 15$$

This will give an indication of separation of the peak maximum, but will not indicate if the peaks have a satisfactory separation. Before we look at separation let us look at the effect of the length of the column on the shape of the emerging peak.

6.1.1.2 Shape of Elution Curves

We can discover the shapes of the peaks by using equation 3. Because we are concerned with a fast elution and the number of plates in the column defines the number of volumes of gas that must be added before any sample emerges, we shall be concerned with small values of N. The factor $\frac{(r-1)!}{N!\,(r-1-N)!}$ will not get large.

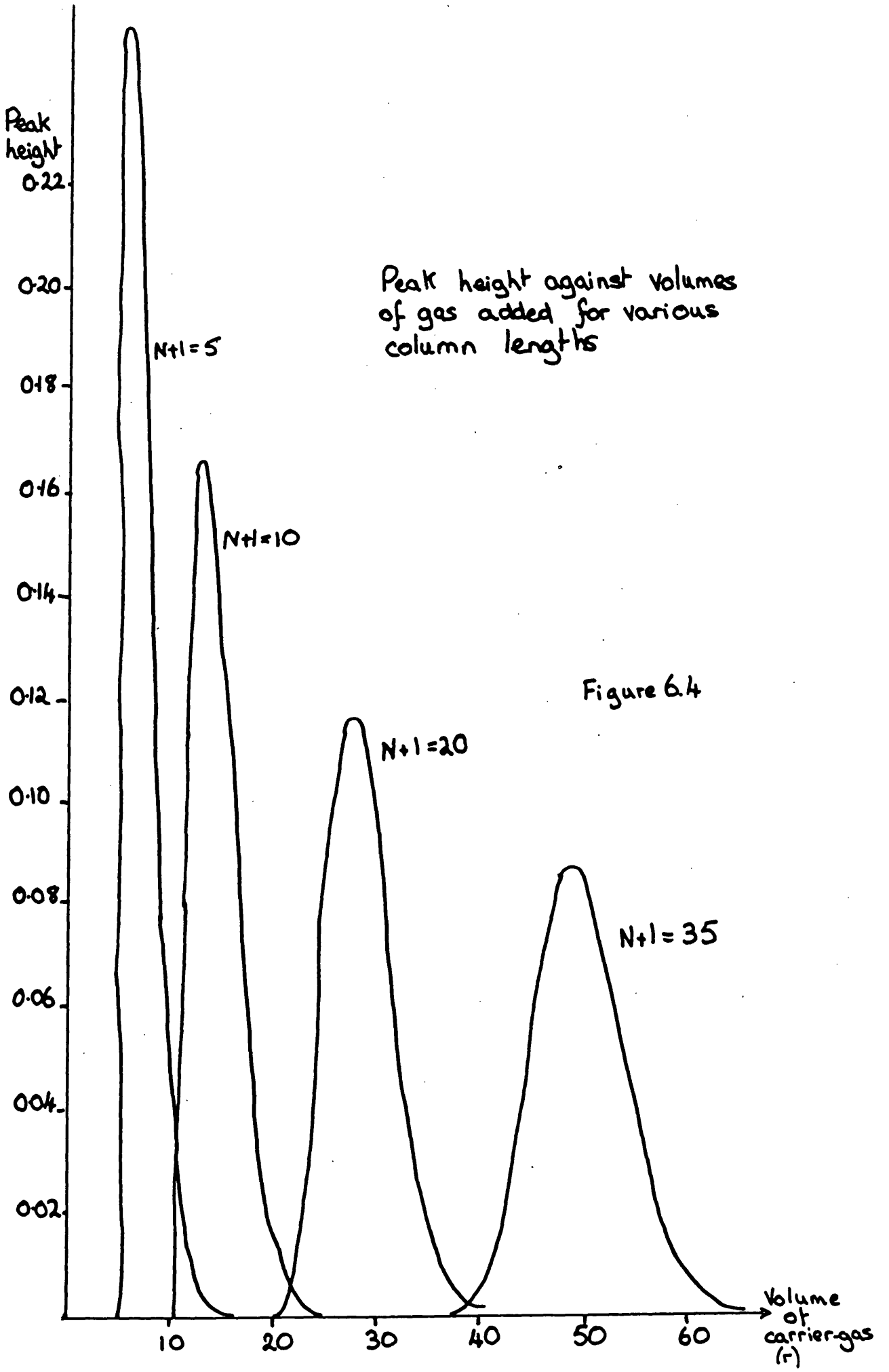
The approximations which may be used when the values of N and R are large are not applicable in this case.

Figure 6.4 shows the shape of the elution curve as N increases. At large values of N the curve approaches the Gausian curve.

6.1.1.3 Separation of Peaks

If 2 substances are in the sample, as we can consider the mixture of anaesthetic and the other gases, then the quantity emerging is the sum of the 2 acting independently.

$$Q = \frac{(r-1)!\ (1-\not{Z}_{air})^{r-N-1}\ \not{Z}_{air}^{N+1}}{N!\,(r-1-N)!} + \frac{(r-1)!\ (1-\not{Z}_{anaes})^{r-N-1}\ \not{Z}_{anaes}^{N+1}}{N!\,(r-1-N)!} \qquad \ldots\ldots\ldots\ldots 16$$



Peak height against volumes of gas added for various column lengths

Figure 6.4

To give a realistic impression of the separation of the anaesthetic from the other anaesthetic circuit gases we will take $\mathcal{Z}_{anaesth} = 0.2$, and $\mathcal{Z}_{air} = 0.7$ at 20 °C, the derivation of this will be shown later. The other gases will be present in say 97% concentration, and the anaesthetic in say 3%; so we will scale the responses by these factors. The detector is more sensitive to the anaesthetic than the other gases. The ratio of the response to halothane and nitrous oxide is 1220:220, when using air as the carrier gas. This gives

$$Q = \frac{(r-1)!\ (1-0.7)^{r-N}\ (0.7)^{N+1} \times 220 \times 0.97}{N!\ (r-1-N)!} + \frac{(r-1)!\ (1-0.2)^{r-N}\ (0.2)^{N+1} \times 1220 \times 0.03}{N!\ (r-1-N)!} \quad \ldots\ldots\ldots 17$$

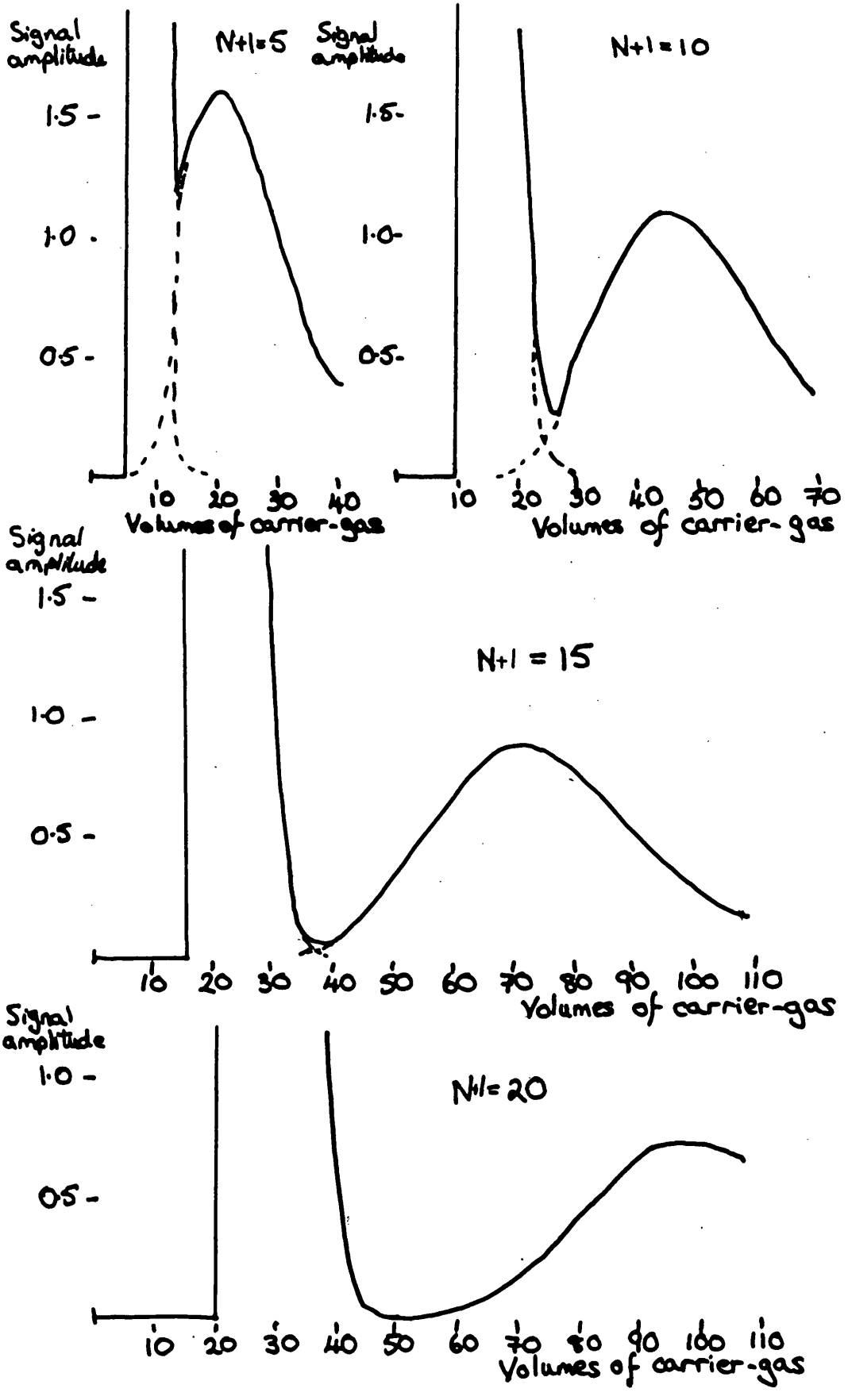
Figure 6.5 shows the effect of the number of plates in the column on the separation as calculated from equation 17.

As is clearly shown the more plates the better the separation, but a longer time will be required. For a separation to be considered satisfactory depends on whether the peak area, or the peak height, is measured. If the area is measured then, obviously, the peaks will have to be better separated than if the peak height is to be measured.

This discontinuous model of chromatography gives a good feel for chromatography. The continuous model gives a different view.

6.1.2 Rate Theories of Chromatography

The theoretical plate theory as outlined in the preceding section was applied to the simple model of a linear ideal process. Gas chromatography may more accurately be considered as linear but non-ideal. The partition isothermal may still be linear, but equilibrium between the phases is not immediate. Various diffusional processes contribute to band spreading.



Effect of column length on separation Figure 6.5

The spreading of a peak is composed of 3 components; diffusional spreading, eddy diffusion and resistance to mass transfer. Their contribution to the height equivalent to a theoretical plate (H) is in an additive manner.

6.1.2.1 Diffusional Spreading

Although solutes pass through the column at different rates, they each spend on average the same length of time in the gas phase. The differences in retention time depends on the time they spend in solution in the liquid phase.

While the sample is in the gas phase self diffusion will take place, that is, the sample will try to eliminate the concentration gradient. The gradient exists because the sample is introduced as a sharp, narrow plug into the carrier gas.

It is shown in Purnell (1962) that the diffusional spread component of the height equivalent to a theoretical plate is inversely proportional to the carrier flow rate

$$\text{that is } H = \frac{B}{\overline{U}} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 18$$

where B is the constant of proportionality and $\overline{U}$ is the carrier gas velocity.

6.1.2.2 Eddy Diffusion

The column packing is likely to be non-isotropic, so across any plane at right angles to the direction of flow the channels through which the gas flows will be of varying size. Some longitudinal spreading of the plug will occur since the time taken to pass through narrow channels will be greater than for the passage through wider ones. The amount of spreading of the molecules is a constant fraction of the

transit time (Purnell 1962), thus the contribution to H is a constant (A)

$$H = A \qquad \text{.................................... 19}$$

6.1.2.3 Resistance to Mass Transfer

This involves material flowing between 2 phases in contact and doing so at least in part by diffusion. The movement results from an effort towards equilibrium, and the rate of movement is determined by the displacement from equilibrium. The closer a system is to equilibrium the slower it moves.

The derivation of the contribution of the resistance to mass transfer to the height equivalent of a theoretical peak relies on a number of assumptions, including the column containing a sufficient number of plates. This may not be present with the short column that will be used here.

Purnell (1962) gives the contribution as being proportional to the carrier gas velocity

$$H = C\,\overline{U} \qquad \text{.................................... 20}$$

6.1.2.4 Simplified Van Deemster Equation

Combining equations 18, 19 and 20 in an additive manner gives the total effect of the contributions and is called the simplified Van Deemster equation

$$H = A + \frac{B}{\overline{U}} + C\,\overline{U} \qquad \text{.................................... 21}$$

Generally we require to have narrow peaks in order that the peaks may be separated easily.

6.1.2.5 Approach to Fast Analysis

If the simplified Van Deemster equation is plotted as H against $\overline{U}$, a hyperbola results with some minimum value of H at some velocity $\overline{U}min$.

$$\frac{dH}{d\overline{U}} = -\frac{B}{\overline{U}^2} + C \qquad \ldots\ldots 22$$

for minimum $\frac{dH}{d\overline{U}} = 0$ $\qquad \ldots\ldots 23$

$$\overline{U}min = \left(\frac{B}{C}\right)^{\frac{1}{2}} \qquad \ldots\ldots 24$$

$$Hmin = A + 2(BC)^{\frac{1}{2}} \qquad \ldots\ldots 25$$

However we are not really looking for maximum efficiency which would be achieved with Hmin, but the efficiency should be minimised in the minimum time so rather than Hmin we are interested in $(H/\overline{U})$ min.

Re-writing the simplified Van Deemster equation

$$\frac{H}{\overline{U}} = \frac{A}{\overline{U}} + \frac{B}{\overline{U}^2} + C \qquad \ldots\ldots 26$$

so $\left(\frac{H}{\overline{U}}\right)_{min} \geqslant C$ $\qquad \ldots\ldots 27$

since as $\overline{U} \rightarrow \infty$ $H/\overline{U} \rightarrow (H/\overline{U})$ min, so we should aim to minimise C where

$$C = \frac{2 K df^2 \overline{U}}{3 (1 + K)^2 D_1} \qquad \ldots\ldots 28$$

Purnell (1962)

Where df is the effective thickness of the liquid layer, D_l is the diffusion coefficient of the solute in the liquid phase, and k is the partition coefficient. So we look for a thin film, a high partition coefficient and a high value of the diffusion coefficient of solute in the liquid phase.

6.1.3 Review of Theory

The discontinuous model gives an insight into the effect of the column length (in terms of number of theoretical plates) on the shape of the peak. The Van Deemster equation illustrates the factors affecting the width of the peak. We will not be using the equations to calculate an ideal solution as many of the values which contribute to the equation are not readily available. However, the equations will be used after a trace has been taken to direct the way towards a better solution.

Having taken a look at the theory, let us now examine the practical implementation of gas chromatography using the theory developed to aid our search for a cold running,fast separation of the anaesthetic from the other anaesthetic-circuit gases.

6.2 Column Parameters

As previously stated the column consists of a tube packed with inert granules which have been coated with a non-volatile liquid. The parameters that may be chosen are:- the column materials and length, the temperature of operation and the carrier gas. In some cases there are restrictions on these parameters imposed by the use of the column in the operating theatre.

6.2.1 Column

When deciding the composition of the column there are several choices to be made. These include: which solvent to use, the thickness of the solvent, the support material, the size of the support particles and the material, the length and diameter of the tube.

It is important that all materials used in the column are inert at the temperature that they are to be used at.

6.2.1.1 The Liquid Phase

The liquid phase should have a low volatility at the column temperature, that is its apparent saturation vapour pressure should be less than 10^{-2} mm Hg (Purnell 1962). Values significantly greater than this will lead to short column life owing to bleeding of the liquid phase. The liquid should also be thermally stable and inert. It would be undesirable for the solvent to react with the carrier gas or sample, though at the temperature that it will be working at, which is low by chromatography standards, there should be no trouble with common chromatographic solvents.

Although there are some pointers on the selection of solvent, such as like dissolves like, there are no set rules. Generally in chromatography one would look for a solvent that dissolved all the components of a mixture. This would allow all the components to be separated provided the solubilities differed slightly. All that is required here

is that the anaesthetic is separated from the other anaesthetic circuit gases. A solvent that just dissolves the anaesthetic and leaves the rest undissolved will be satisfactory.

Since the halogenated hydrocarbon anaesthetics are polar it is expected that the solvent will be polar. As there are no hard and fast rules, it was decided to conduct a literature survey to pick out the use of gas chromatography to separate anaesthetic-circuit gases.

Purnell (1962) gives a list of widely used solvents and the sample types for which they have been used. Halogenated hydrocarbons occur only under silicone oils and greases, though "all types of aliphatic hydrocarbons" occur under apiezon grease, polyglycols, di-alkyl phthalates and squalane. The only commonly used solvent that does not have a classification which could include the anaesthetics is tri-cresyl phosphate. As this survey did not yield a specific solvent but a range of possibles, it was decided to conduct a small survey of columns reported which have been used for separating anaesthetic circuit gases.

Appendix C shows the result of this survey. It can be seen that the above useful solvents are included with the exception of polyglycols (although the survey is not exhaustive). Silicone fluids are well represented both as MS550 and Kel-F-Oil. It was decided to use a silicone fluid and to base the column on one of the columns shown.

The column should operate at room temperature or slightly above, and give the separation quickly. Although there is no column represented that gives the separation fast enough and at the temperature required, the Patzlova's system (last entry in Appendix C) operates at room temperature and the halothane emerges in about 2 minutes. So it was decided to base the column on this. By doing so it is hoped to be able to make up a column with a reasonable chance of success.

6.2.1.2 Patzelova's Separation

Patzelova makes use of 2 columns in order to separate all the gases from each other. The system is shown in Figure 6.6. The action of the first column is to separate the anaesthetic from the other gases. The second column separates the oxygen, carbon dioxide and nitrous oxide. The trace produced by this system is shown in Figure 6.7.

In our case only the effect of the first column is required and as the separation of nitrous oxide takes about 6 minutes, it is estimated that the separation of halothane from the other gases by the first column takes about 2 minutes. This is longer than we can afford, but a suitable starting point.

So, as a first solution we will base the column on the Patzelova first column, that is 80-100 mesh Chromosorb W NAW coated with 15% by weight of Kel-F-Oil.

6.2.2.2 Tube Material and Dimensions

The tube, into which the solvent coated solid support is packed, needs to be inert to all the compounds with which it is expected to come into contact. Stainless steel and glass are commonly used. We chose glass merely from convenience. The packing is held in place by plugs of glass wool.

The internal diameter of the tube was chosen to be 4 mm to match the Patzelova column. The column length will be determined experimentally. Obviously the longer the column, the longer the sample will take to elute at a particular carrier-gas flow-rate so a short column will probably be required.

6.2.3 Carrier Gas

It is desired to make the meter, which will use the column, as compact and easy to use as possible, so we are limited to air as the carrier gas. If the air in the operating theatre is used as the carrier

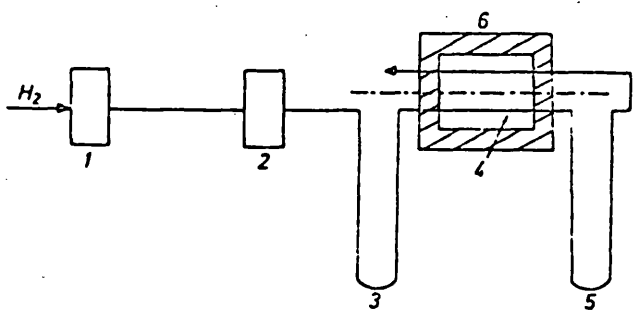


Fig 6.6

Patzelova's

System

o The function scheme of the chromatograph used.

1 = the needle microvalve
2 = the sampling valve
3 = the first column
4 = the thermal conductivity detector
5 = the second column
6 = the thermostatic oven of the detector

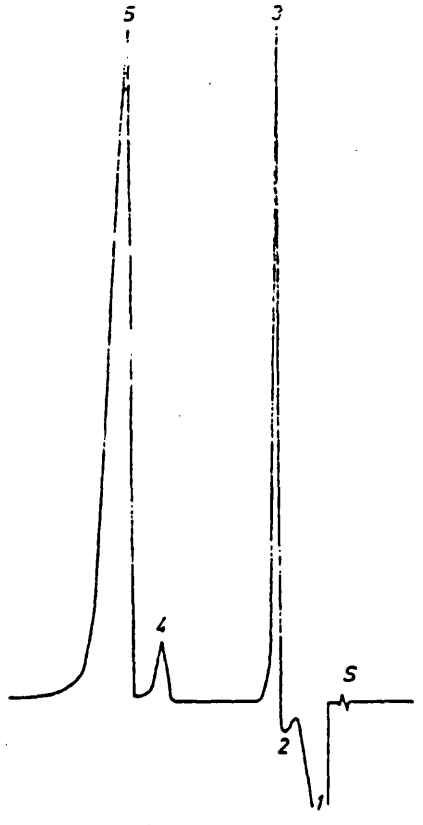


Fig 6.7

Separation by

Patzelova's

System

o The separation of the Halothane, O_2, CO_2, N_2O

1 = $O_2 + CO_2 + N_2O$
2 = Halothane
3 = O_2
4 = CO_2
5 = N_2O

gas, then no external connections will be required, that is, no bottled or piped supply is needed. Provided care is taken to ensure that the air inlet is not near a source of anaesthetic pollution this air should provide a satisfactory carrier gas. The average concentration of pollution is likely to be less than 4 parts per million (Cohen 1980), so this will not affect the measured concentration. Changes in the composition of the air will result in an internal base line drift which is easily compensated for.

6.2.4 Temperature

Often in gas chromatography high temperatures are used to speed the separation. At high temperatures the components will be more mobile and pass through the column quicker. In our case it is undesirable to raise the temperature above about blood heat. This is because there could be an explosion hazard with flammable anaesthetics if the column temperature was higher. The hazard would arise from the theatre atmosphere, or anaesthetic circuit gases being in contact with a hot source.

In practise the low temperature requirement presents no problem. This will be shown in the next chapter. The column could give an adequate separation at 10 ^{o}C, which is less than the usual room temperature. However, as the temperature affects the separation, both the peak height and the time of separation, it will probably be necessary to thermostat the column at about 30 ^{o}C to ensure stability. It is obviously much easier to heat the column and maintain a slightly elevated temperature than to refrigerate it to maintain a slightly depressed temperature relative to the expected range of ambient temperature.

6.2.5 Review of Column Parameters

The column chosen for initial study is a glass tube 4 mm internal diameter packed with 80-100 mesh Chromosorb W NAW coated with 15% by weight Kel-F-Oil. The length of column is to be determined experimentally. The carrier gas is to be air and the column may be thermostated at 30 ^{o}C.

Having chosen the column materials we must now look at detectors and gas sampling valves.

6.3 Detectors

Detectors sense a change in the composition of gas coming from the column. There are 3 detectors that are commonly used in gas chromatography; the flame ionization detector, thermal conductivity detector and the electron capture detector. There are several types which are not so commonly used. However, none of the detectors are suitable and a refractive index detector was used. The operation of the detectors and the reasons for their unsuitability are discussed below.

6.3.1 Flame Ionization Detector

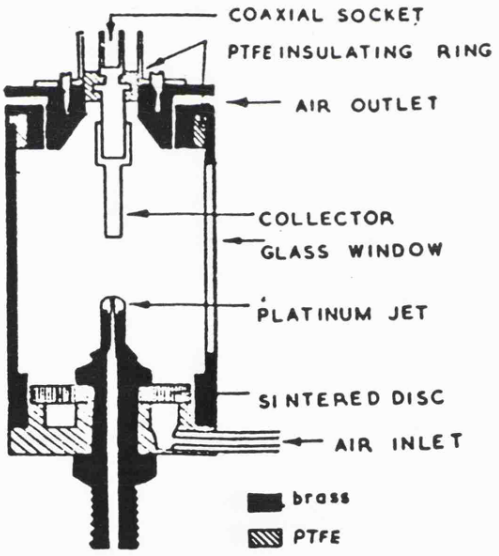


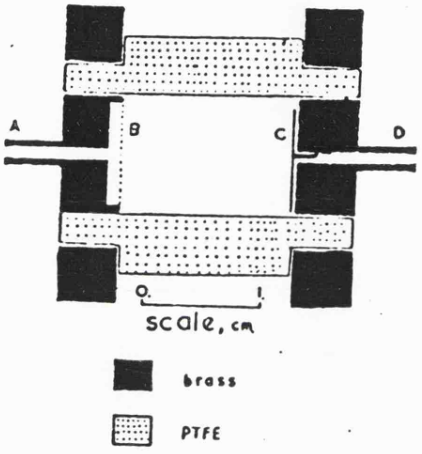
Fig 6.8
Flame
Ionization
Detector

Szymanski (1962: 91-94)

This detector is the most commonly used one in gas chromatography. It consists of a burning jet of hydrogen, carrier gas and elutant. A platinum electrode, at a potential of about 300 v across the electrodes collects the ions formed by combustion. The detector is not affected by small changes in temperature or pressure but careful control of the

hydrogen and air flow rates is needed. The detector does not respond to carbon dioxide, oxygen, nitrogen or nitrous oxide. Water vapour causes instability. Although this device is particularly suited to the analysis of hydrocarbons the flame and high voltage precludes it from use in the operating theatre.

6.3.2 Electron Capture Detector



A Inlet for carrier gas and anode
B. Diffuser made of 100 mesh metal gauze
C. Tritium source of ionizing radiation
D. Gas outlet and cathode

Fig 6.9
Electron Capture Detector

Thermal electrons are set free by collisions between soft β-particles from the tritium source, and an inert carrier gas, eg nitrogen. A neutral sample molecule with an affinity for electrons may be ionised. A voltage is applied across the cell in order to collect the ions and electrons. An ion is slower moving and has a higher chance of recombining than a free electron, so the current flowing through the cell is reduced by the presence of the sample molecule.

The device may be used in a variety of modes, Lovelock (1963) lists the following: an ionization cross section detector, a detector

employing a metastable ionization process and an electron mobility detector in a pulsed or dc mode. It is a selective detector and responds particularly well with chlorinated compounds (Aue 1975) such as halothane. It needs a very clean carrier gas supply, preferably argon, nitrogen or helium free from contaminating oxygen. It is extremely sensitive to some trace impurities. Non-linearity may occur because of these contaminants or column bleed. For these reasons it is necessary to run standardisation samples from time to time.

It is undesirable to make use of radio active sources, even low energy ones such as this, in the theatre if this can be avoided and some of the modes require high voltages. For these reasons it was decided not to use the electron capture detector.

6.3.3 Thermionic Detector

This is another common type of detector used in gas chromatography. It consists of 2 thermistors, one placed in a reference gas stream and the other in the elutant. The difference in thermal conductivity of the 2 streams is measured, usually by using the thermistors in a Wheatstone Bridge arrangement.

The position of the thermistors and shape of the cell affects the shape of the eluted peak. Lochmuller, Gordon, Lawson and Mathieu (1977) discuss the effect in their paper. The thermionic detector is readily adaptable to varying needs. It is commonly used on "standard" size chromatographs and made in a subminiature version whose size is 0.375" x 0.375", Wilhite and Kruger (1965). It can work from low voltages and the heating current for the thermistor is small. It was thought that this detector would be suitable, but when one was made the signal to noise ratio was poor and it was extremely flow sensitive.

The following detectors are ones that are not commonly used.

6.3.4 Piezoelectric Sorption Detector

Piezoelectric crystals have long been used as frequency and time standards, but they are also used as accelerometers, to measure the thickness of evaporated films and to measure the absorption of gases by quartz. These last 3 measurements depend on the frequency change of the oscillations of the crystal caused by sensitivity to weight acting on its surface. By coating the surface of the crystal with a liquid phase, a frequency change may be obtained as the elutant passes over and partitions into the liquid phase. The resulting frequency may be compared with a reference frequency and the frequency change due to the elutant obtained (King 1964).

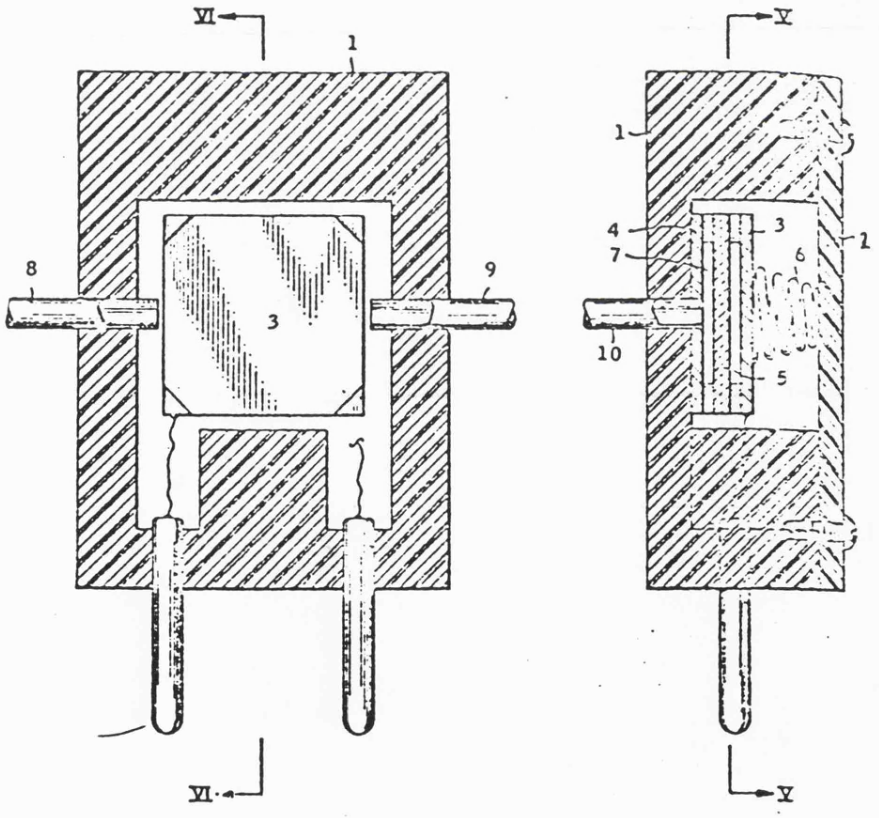


Fig 6.10 Piezoelectric Sorption Detector

1. Bakelite holder, 29 × 21 × 11 mm., FT-243
2. Front cover fastened with screws
3. Front electrode
4. Rear electrode with 2-mm. diameter gas tube connection
5. 1.2 × 1.2 × 0.02 cm. quartz crystal
6. Spring to maintain contact pressure
7. Detector volume of about 0.02 ml.

8,9,10. Rear and side gas tubes

According to Janghorbani and Freund (1973) this detector has a highly linear function of peak height to sample volume.

It was thought that this detector would have poor long term stability, due to contaminants deposited on the surface causing base line drift and bleed of the coating which would cause a change in sensitivity.

6.3.5 Gas Density Balance

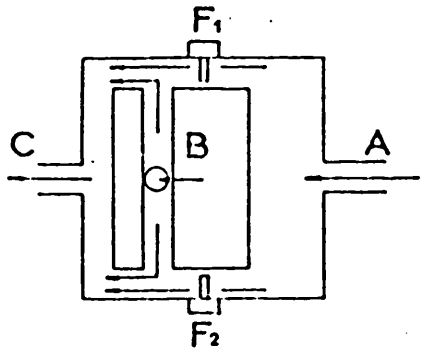


Fig 6.11.
Gow-Mac Gas Density Balance

The original design of a gas density balance by Martin and James (1956) was one of the first types of detector used in gas chromatography. However, it was extremely difficult to produce and fell into disuse. The design was simplified by Guillemin and Auricourt (1963), and came into wider use as the Gow-Mac Gas Density Balance. A reference gas enters at A in Figure 6.11, and the sample gas at B; they share the exit at C. If the gas entering at B has the same density as the reference gas then equal amounts go through the flow meters F1 and F2. If the gas at B is more dense, more of it will go to the bottom and hence reduce the flow through F2 and increase the flow through F1. Similarly if the sample gas is less dense than the reference then more will flow through the upper branch, reducing the amount of reference flowing through F1, and increasing the amount

through F2. This detector is suitable for corrosive gases as the sample only flows from B to C, the walls of which may be specially constructed; the sample gas does not flow through the flow meters. It has a fast response to changes in the sample gas, but the detector is sensitive to shaking and must be mounted the right way up as it depends on gravity. It works best with either argon, nitrogen or carbon dioxide as reference gas. This device appears to be too delicate for use in an operating theatre.

6.3.6 Absolute Mass Integral Detector

This detector, developed by Bevan and Thorburn (1965), is based on the absorption of the elutant on activated charcoal. The absorption produces a change of weight of the sample cell which is measured. The semi-permanent absorption of the elutant gives a step up as each substance is eluted. The rise in height of the step is due to the weight of that particular substance absorbed.

The absolute Mass Integral Detector has the obvious disadvantage of needing to be frequently reactivated, and as such is not practical for this purpose.

6.3.7 Pneumatic Gas Chromatographic Detector

Described by Annino and Voyksner (1977) it employs a 0.002 in diameter orifice in series with the capillary column. It generates pressure signals as sample components emerge from the column and pass through the detector, and detects changes in the density and viscosity of the elutant. Developed as a totally pneumatic based system it would require a transducer to convert the pneumatic output to electrical output, unless a pneumatic gauge with sample and hold facilities could be found.

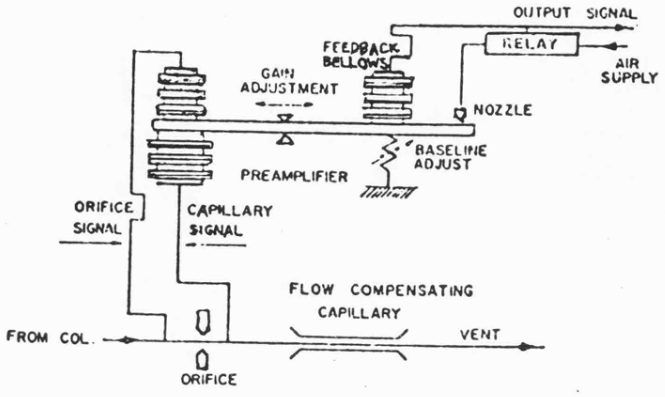


Fig 6.12

Although this detector could be used it was felt that it was over complicated.

6.3.8 Refractive Index Detector

Having exhausted the commonly used, and some of the less commonly used, detectors without finding a wholly suitable one, it was decided to try a detector which measured the refractive index of the elutant. Refractive index measurement is frequently used for determining the concentration of anaesthetic with a known gas or fixed gas mixture, for instance, to calibrate vaporizers. It has not, to my knowledge, been used in Gas Chromatography. However, it has been used in Liquid Chromatography (Johnson, Campanile and Le Febre, 1967). This particular device measures the intensity of light reflected from a glass-sample interface. It is said to be sensitive to a change of 1×10^{-6} refractive index units, and drift usually corresponds to less than 5×10^{-6} units for an 8 hour period. This method is suitable for liquids which have a comparitively high refractive index of the order

of 1.5 in the range 1.333 for water, to 2.2 for mercury iodine in aniline (Kaye and Laby pub 1959). It would be unsuitable for gases with their low refractive index; 1.000035 for helium to 1.002675 for cadmium vapour as the extreme values. Going from the lowest refractive index to the highest in liquid is a change of almost 100%, while for the gases it is about 0.2%. Thus devices that measure proportional to the absolute value of refractive index are satisfactory for liquids, but would not be satisfactory for gases as the measurement would be lost in the limit of sensitivity. It is better for gas measurement to make use of a system where the difference between a sample and a reference gas is actually measured. By suitable choice of reference gas a satisfactory percentage change may be observed.

6.3.8.1 The Zeiss Interferometer

This is a manufactured, commercially available refractometer generally used for the measurement of firedamp (methane) in mines. The fringe pattern moves across the calibrated scale and the refractive index of the "air" may be measured.

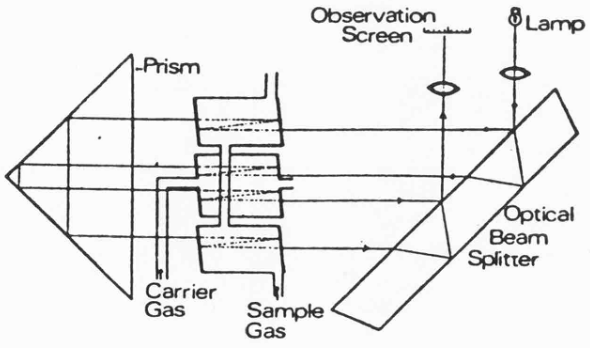
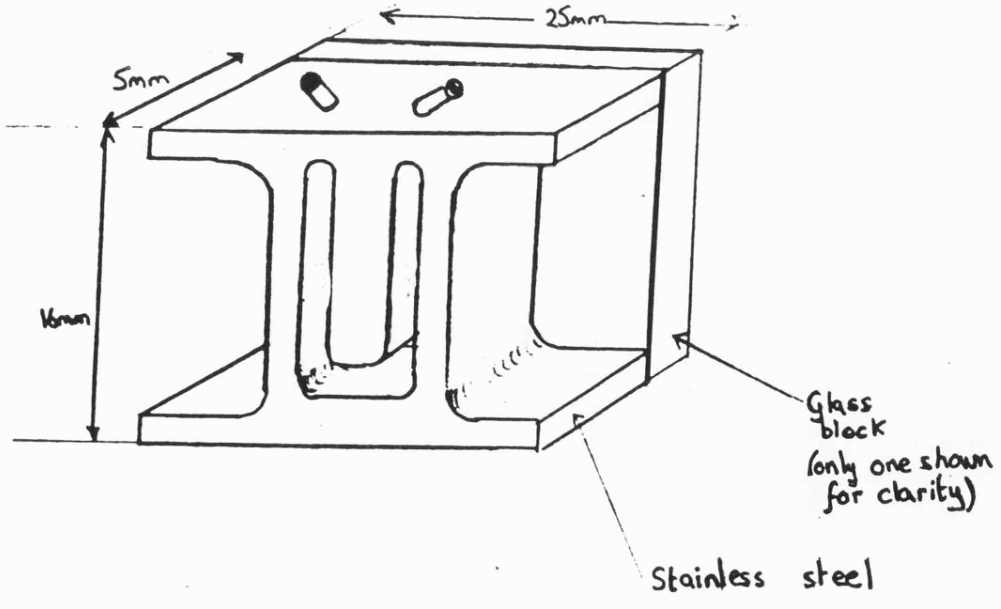


Fig 6.13
Schematic of Zeiss Refractometer

The Zeiss Interferometer Schematic shown in Fig 6.13 makes use of only one glass block which has the dual purpose of splitting the beam and rejoining it.

A fringe pattern is initially produced by tilting the prism. This causes a displacement of the 2 beams from each other after they have hit the glass block for the second time. The lens brings these beams to the focus and the fringe pattern is produced by the constructive and the destructive interference of the beams. Having produced a fringe pattern movement is caused by a change in the refractive index of the sample. This movement is detected by 2 photocells.

The original sample cell was removed. It had silvered panels to reflect the beams back and forth through the sample so that the beam travelled a total of 6 times through the sample. We felt we would not need this extra sensitivity, and also wanted to reduce the sample-cell volume. The sample-cell was replaced with a simpler cell through which the beam passed twice.



Not drawn to scale

Fig 6.14
The Sample Cell

The sample-cell volume is 0.4 cc. It is made of stainless steel with the original glass plates (with the silvering removed) glued on.

This detector has the advantage over the other commonly used detectors in that it does not use high voltages, radio activity or flames. Also the anaesthetics are known to have high refractive indecies compared with the other anaesthetic circuit gases.

6.3.8.2 Electronics Associated with the Refractometer

To get the movement of the fringes into a usable electrical signal some electronic circuitry is required. Further circuits are required to select the peak of interest and either the peak height or area. Also to hold the result obtained until it can be refreshed with an up dated version of the signal.

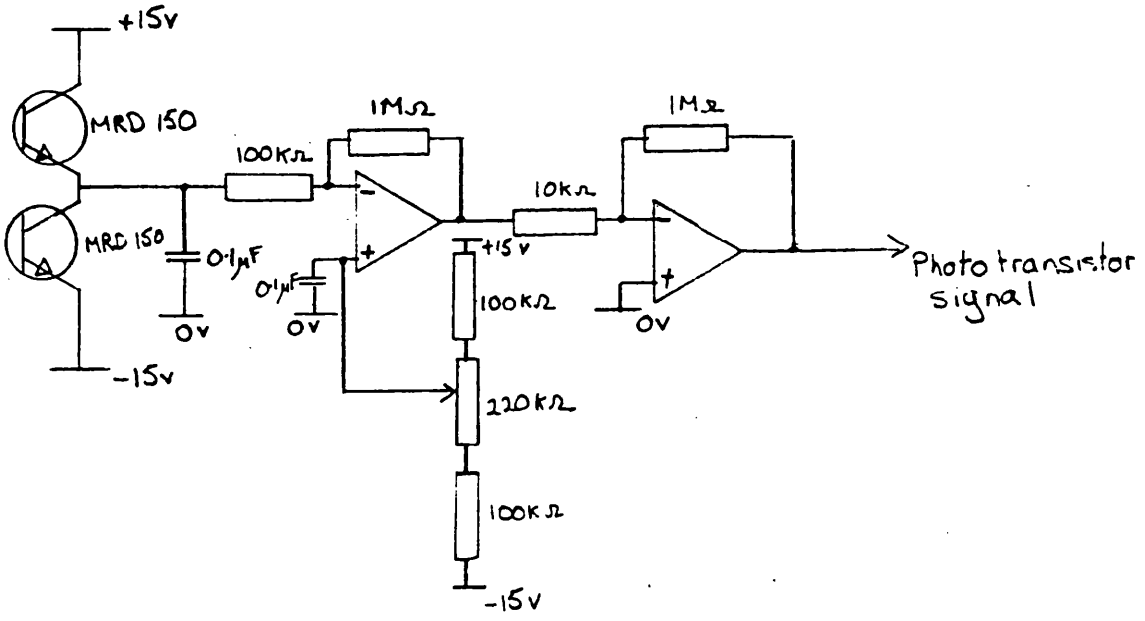


Fig 6.15

Photo Transistor

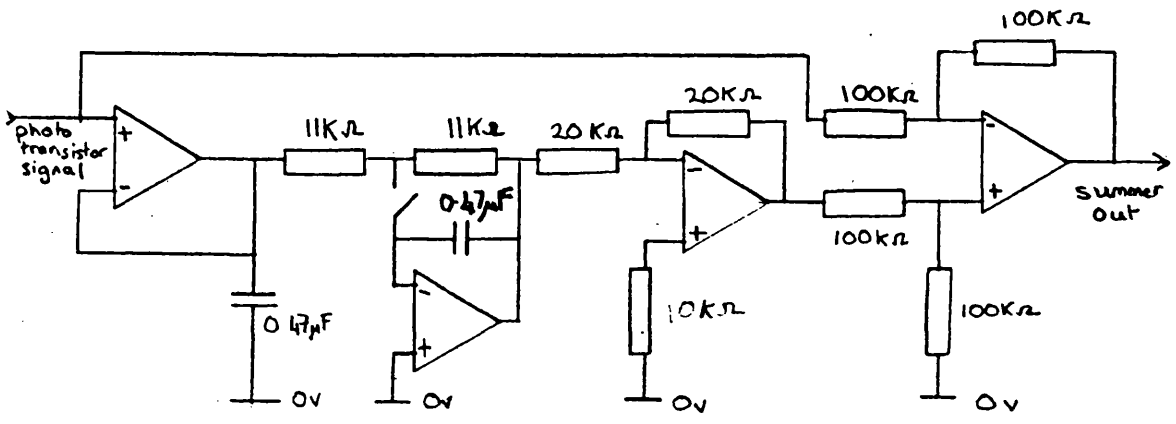


Fig 6.16

Line Drift Compensation

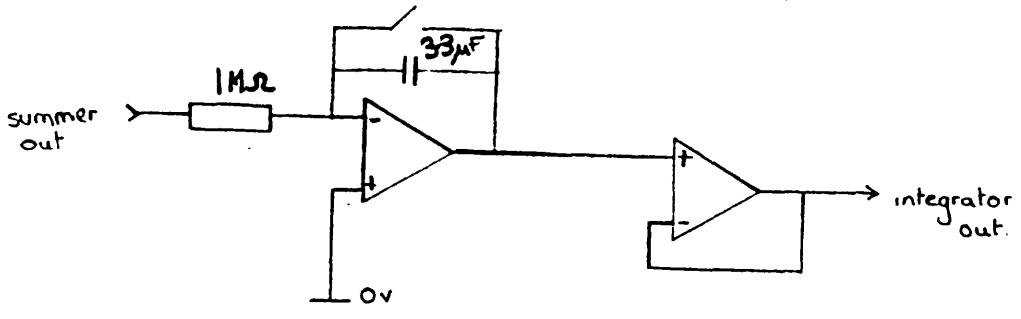


Fig 6.17

Integrator

Fig 6.18

Peak Value

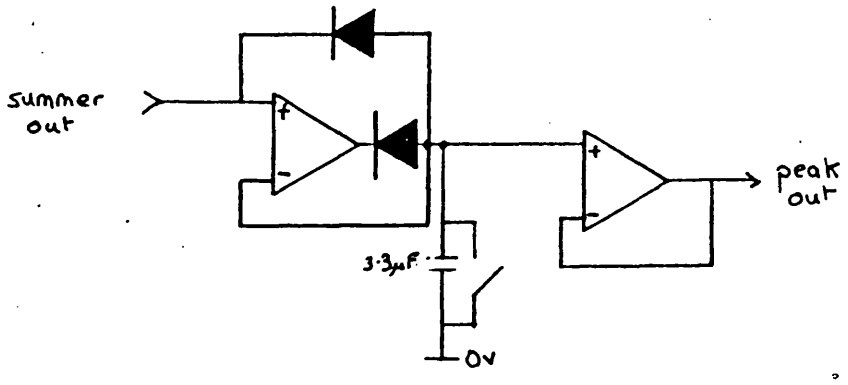
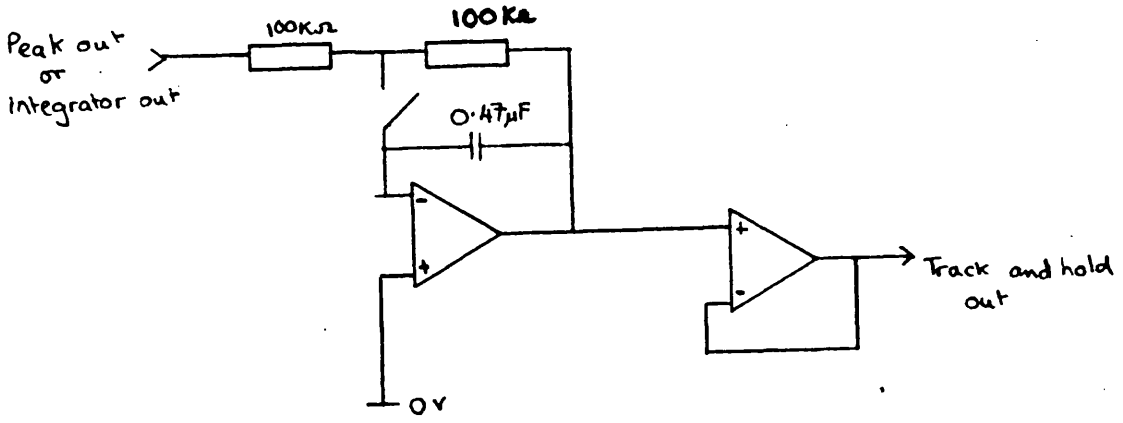


Fig 6.19

Track and Hold



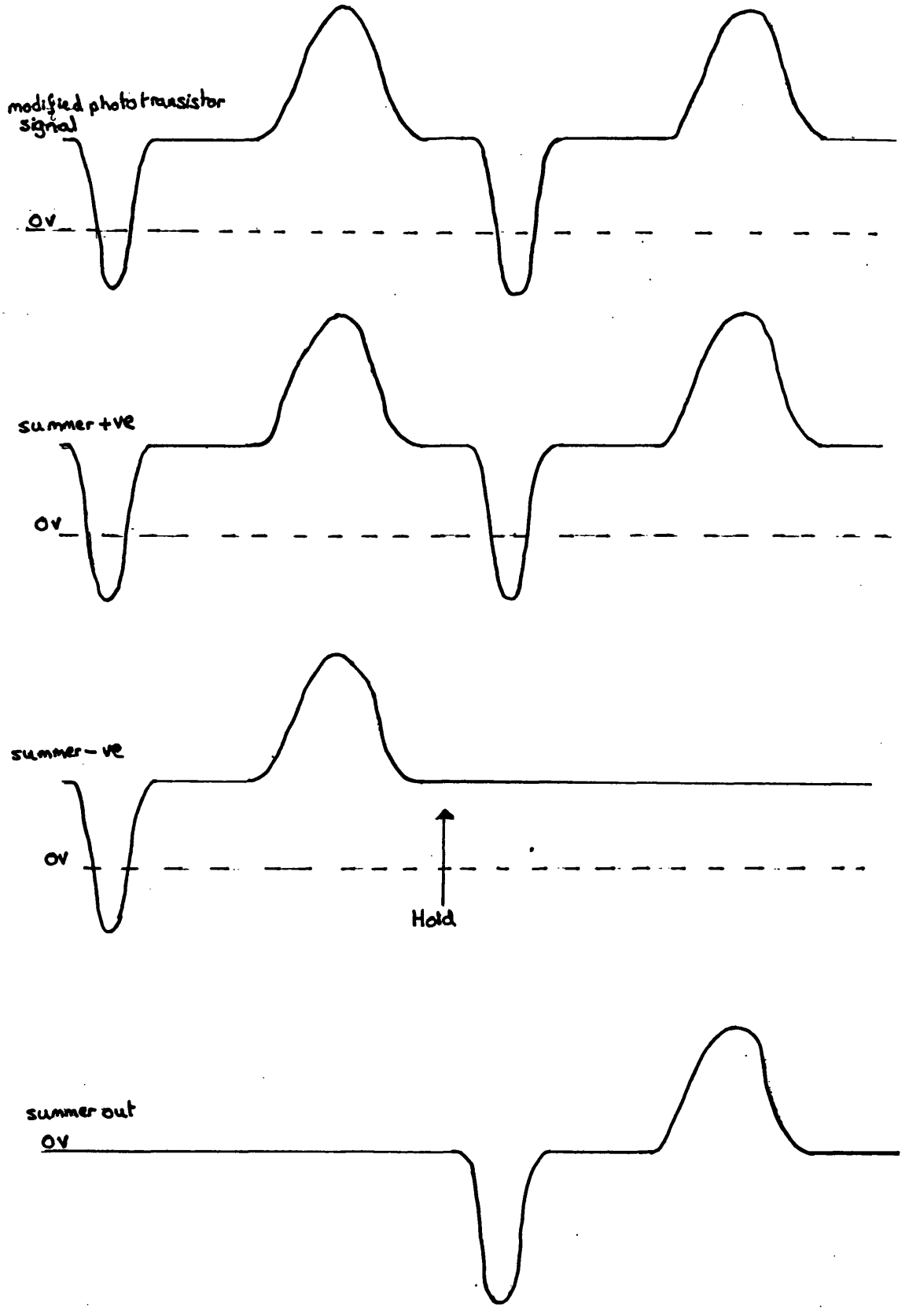


Fig 6.20 Waveforms Before and After Base Line Compensation

6.3.8.2.1 Photo Transistor Circuit - Figure 6.15

The 2 photo transistors are connected in series between the positive and negative rails. The photo transistors should be "looking" at different parts of the fringe pattern and movement of the fringe pattern will cause a change in the current that is delivered to the 100 KΩ resistor.

This goes into the negative input of a differential amplifier. The positive input is supplied with a variable voltage which allows for an adjustment of dc level so that the following differential amplifier will not be saturated. This differential amplifier with negative feedback gives a 100 times gain. A variable gain could be employed in practice to accommodate different sensitivites. Its output is the modified photo transistor signal.

6.3.8.2.2 Base Line Drift Compensation - Figure 6.16

The modified photo transistor signal feeds along 2 paths. The first goes directly to a summer circuit. The other goes via a buffer which feeds into a track and hold circuit. In the tracking mode this circuit has a gain of -1; the signal is reinverted by the next differential amplifier giving the whole line from the modified photo transistor signal to the +ve input of the summer, a nominal gain of +1. Thus, as the summer has equal gain for both sides, the output of the summer will be zero in the tracking mode. When the switch for the track and hold circuit is placed in the hold mode, the capacitor holds the voltage it was at when the switch was activated. Thus the +ve input of the summer is fed the base line. The direct line will now report the modified photo transistor signal. The summer output will be the difference between the base line voltage before operation of the switch and the modified photo transistor signal as shown in Fig 6.20. Thus holding gives the signal movements from zero volts.

6.3.8.2.3 Integrator - Figure 6.17

This follows the summer and simply integrates the input with respect to time from the time when the capacitor is allowed, by the switch, to charge. This is followed by a high impedence buffer whose purpose is to prevent the capacitor discharging through the following device to earth.

6.3.8.2.4 Peak Value Detector - Figure 6.18

This circuit also follows the summer. It will follow the rise of the incoming voltage and store the maximum voltage attained in the capacitor. When the voltage begins to fall, the diodes cease to conduct and the capacitor retains the maximum voltage. Again this is followed by a high input impedence buffer to prevent discharge of the peak value.

6.3.8.2.5 Track and Hold - Figure 6.19

This is the same circuit as the one in the base line drift compensation circuit. It may be used after either the peak value detector or the integrator. Its purpose would be to hold the value obtained while a fresh value is prepared. When the new value is ready this is tracked and held. Thus the other circuits are free to reset while the voltage is held and could be displayed.

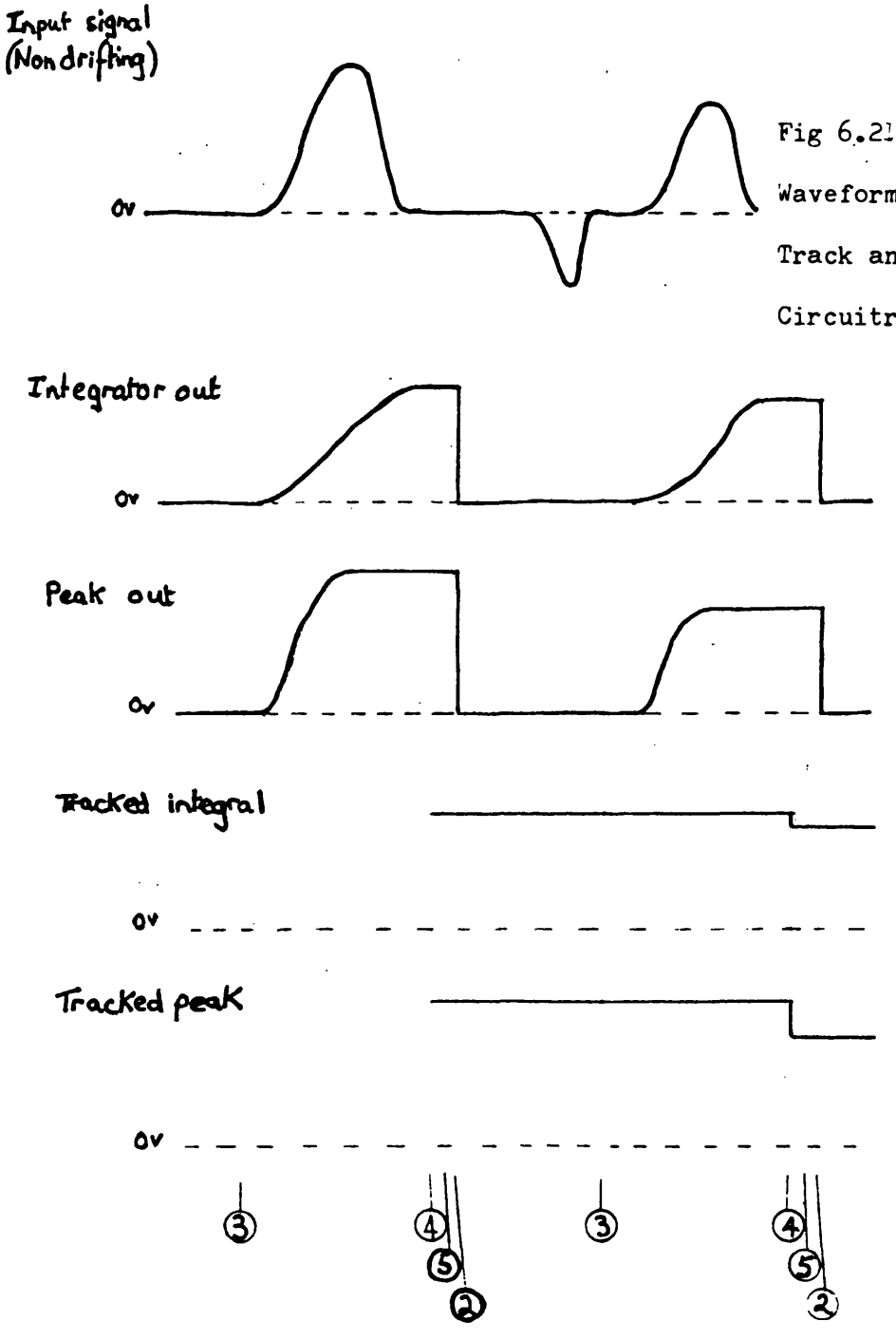


Fig 6.21a Waveforms Illustrating Track and Hold Circuitry

6.3.8.3 Order of Operation

The input signal in Figure 6.21a shows oxygen separated from halothane. The oxygen peak is in the opposite direction from the halothane peak as the refractive index is less than air for oxygen

and greater than oxygen for halothane. When nitrous oxide is used with oxygen, both peaks would have the same sign with respect to the base line. Before commencing measurement the potentiometer would be set so that the modified photo transitor signal would be within the range of the second differential amplifier.

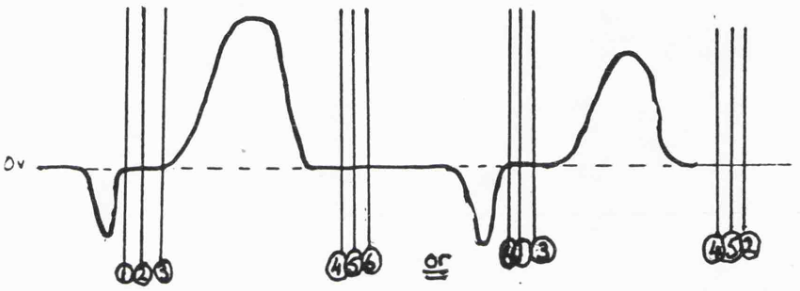


Fig 6.21b Order of Operation Of Switches

(1) Hold base line.

(2) Short circuit integrating capacitor and peak holding capacitor.

(3) Remove short circuit.

(4) Track peak and integral.

(5) Hold peak.

(6) Track base line.

Initially the base line is being tracked; this needs to be held after the air peak has passed. The peak detector and integrator are reset to zero and then allowed to be free to detect. After the peak of interest has passed, the peak value and integral have been measured and the track and hold circuit retains the value. The base line is tracked again and the device is ready for the next peak.

In an operational instrument the timing would be performed automatically by a timing circuit. It would be necessary to know when

the air peak and the peak of interest are expected to arrive in order that the actual timing could be arranged. If the sample introduction were done by the solenoid valve method then the time of sample introduction could be easily observed and the timing of the 3 other sequences would follow from that.

6.3.8.4 Circuit Considerations

It was found necessary to use FET op amps for all the differential amplifiers. This was because other op amps tended to discharge the capacitor and the low input current taken by the FET op amp allowed the charge on the capacitors to remain. In the base line drift circuit compensation was necessary to adjust for zero off-set on the integrator. This was to prevent the small off-set voltage from being integrated by the integrator and appearing as a signal. Both lines to the summer have a nominal gain of one, but could have a slightly different gain. It would, therefore, be useful to put a gain adjust into one of the lines to ensure that the gains were exactly the same. Although this was not done in the circuit and a reasonably satisfactory operation was obtained, better operation would result if this were done.

This detector was found to be very satisfactory with low signal to noise ratio and good sensitivity.

6.4 Gas Sampling Valve

The gas sampling valve introduces the sample gas into the carrier gas stream. Often in gas chromatography the sample to be introduced is in the liquid state and needs to be vaporised before being injected into the column. This is not so in this case as the sample is already in the gaseous state. Determination of the concentration of a component requires a constant sample volume and sample introduction time so that comparisons may be made. Thus, the valve needs to give a repeatable sample introduction.

6.4.1 Specific Requirements

There are constraints on the sample valve material due to the nature of the gases being used. Large volumes of grease and rubber, plastics and similar materials should be avoided as these absorb and may be attacked by halothane (Sadove and Wallace 1962: 10-11). See Appendix A.

Similarly certain metals should be avoided as wet halothane may attack them. See Appendix B.

The valve is required to be automatic in its operation and capable of running for reasonable periods of time (at least a month) without requiring attention.

6.4.2 Survey of Valves Commonly Used

In gas chromatography, apart from syringe injection which is not suitable for automatic operation, there are 2 main types of valves; the linear valve and the moving disk valve.

Linear valves have a fixed cylinder with a number of ports which are separated from one another by a set of seals on a central rod. Movement of the rod between 2 positions causes the ports to be connected in different ways. The first position allows the sample loop

to fill while the column is connected to the carrier gas. The second position causes the sample loop to be flushed of sample, as the column is connected via the sample loop to the column. This introduces the sample into the carrier gas stream.

The moving disk type consists of a fixed part and a moving part. The fixed part has the gas ports. Movement of the other part, which has slots to connect the ports, causes introduction of the sample.

One other typed of valve, a fluidic valve, is described. It is the only other type I have come across and is included for completeness.

In all types of valve except the fluidic valve a sample loop is switched between being connected to the sample supply and vent, and between the carrier gas and column as in Figure 6.22.

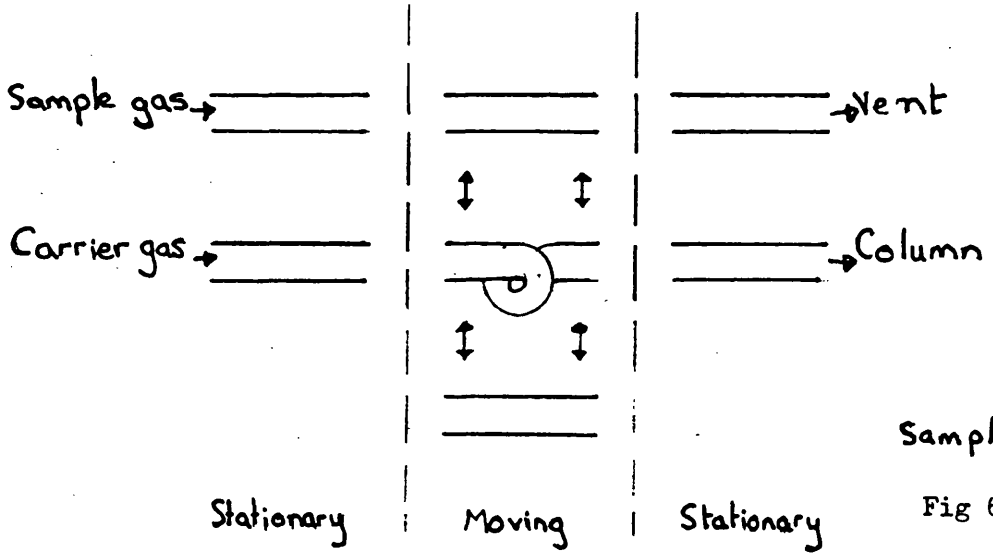


Fig 6.22
Action of the Gas Sampling Valve

The action of the valve may also be conveniently thought of as opening and closing valves.

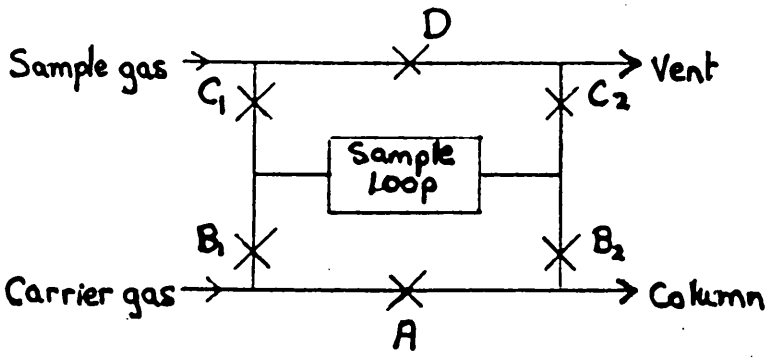


Fig 6.23

Valve Analogy

In Figure 6.23 the valve D is not absolutely necessary since the sample gas does not need to go to vent, but I think it is desirable to keep the sample gas flowing. The crosses represent valves. To fill the sample loop, D is closed (that is not conducting), C is open (that is conducting), B closed and A open, for sample injection C closed, D open, A closed and B open.

6.4.3 Linear Gas Sampling Valve

(Szymanski 1962: 23)

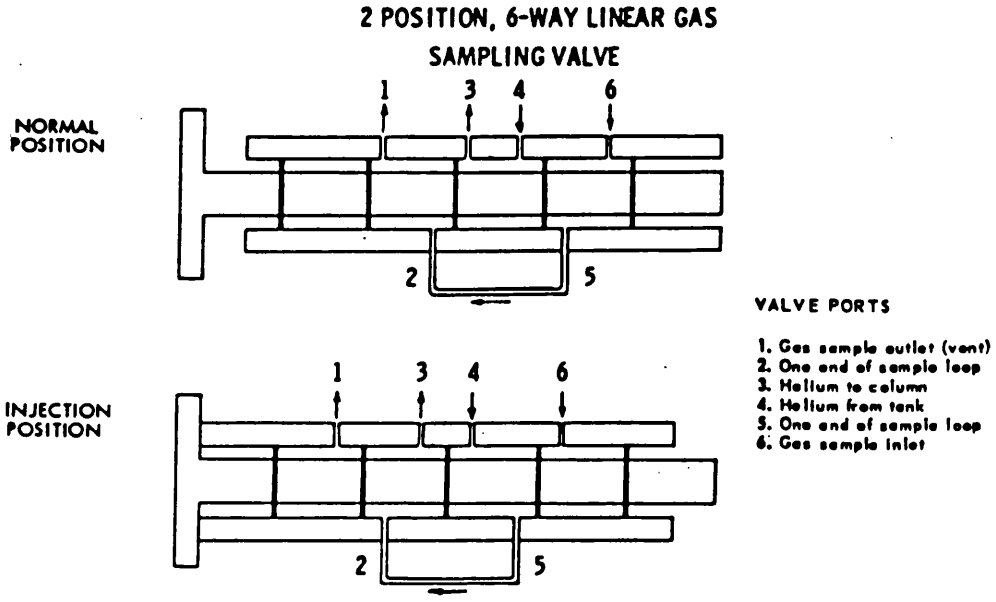


Fig 6.24 Linear Gas Sampling Valve

In the normal position in Figure 6.24 sample gas enters through port 6, passes through the sample loop and leaves from port 1. To inject the gas sample contained in the sample-loop, the plunger is depressed for a few seconds which causes the carrier-gas from port 4 to sweep the sample from the loop through port 3 to the column.

The valve employs rubber to metal O - ring seals which make it leak free. This is not suitable for use in the presence of halothane as the rubber may perish and is likely to swell, which could make movement impossible. In the intermediate position between the normal position and injection position, all the gases are cut off. This is undesirable if fast elution times with a minimum disturbance to the flow rate is required.

6.4.4 Combination Sample Injection and Backflush Valve

Eaton, Umstead and Smith (1973)

Back flushing is a technique used to speed up the elution of a highly retained elutant. Had a satisfactory separation not been obtained, back flushing would be a technique which could have been employed. However, it is useful to study the valve shown in Figure 6.25 as it may be possible to adapt it to suit the application.

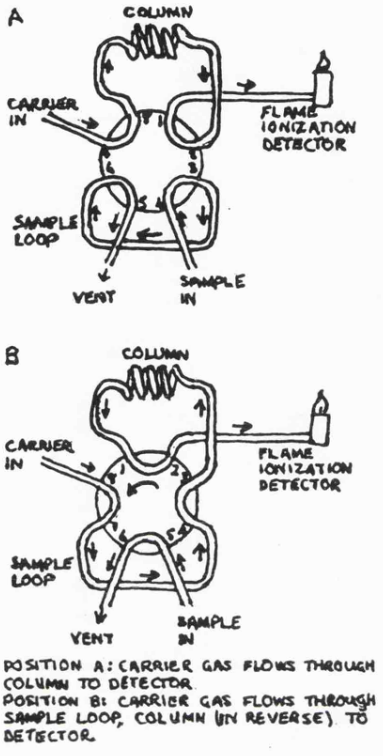


Fig 6.25

Combination

Valve

As with the previous valve, in the intermediate positions no gas will flow. Also, as the valve comes up to the positions shown the gas flow-rate will gradually increase until in position, then as the valve moves past this position the gas flow-rate will decrease. There is a possibility of the valve leaking when the high pressure carrier gas is not connected to the column or via the sample-loop to the column. This leak may be through the sample-loop to the vent, thus washing out or diluting the sample. If the time between introductions of the sample is variable, different amounts will be washed out and the valve will not give a reproducible input and thus will not be suitable for quantitative measurements.

6.4.5 Fluidic Monostable Multivibrator

Gaspar, Arpino and Guiochon (1977)

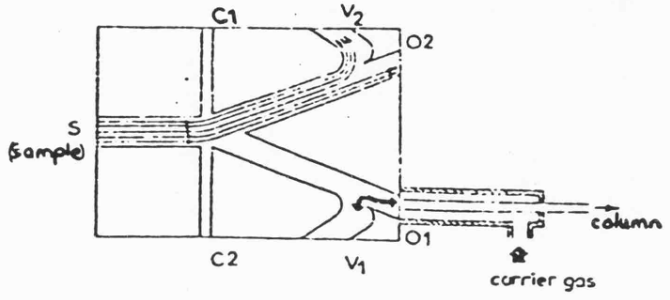


Fig 6.26

Fluidic Valve

The valve in Figure 6.26 is quite an unusual valve. It has the advantage of having no moving parts. Control of the introduction of sample into the carrier gas stream is achieved by use of the command inlets, Control 1 and Control 2. There are 2 signal outlets, Output 1 and Output 2, and 2 gas venting ports, Vent 1 and Vent 2. A truth table for its operation is shown below in Figure 6.27.

Control 1	Control 2	Output 1	Output 2
0	0	0	1
1	0	1	0
1	1	0	1
0	1	0	1

Fig 6.27

Truth Table for

Fluidic Valve

This valve is only used for injection onto open tubular columns. It can provide injection bands with adjustable widths between a few

milliseconds to several tens of milliseconds. Open tubular columns consist of a glass capillary tube, the inside surface of which is coated with the liquid phase. The pressure drop across these tubes is less than the pressure drop across conventional gas chromatographic columns. This type of valve, though suitable for the open tubular columns, will not work at the inlet pressure required for conventional columns.

6.4.6 Automatic Gas Sampling Device

Hill and Hook (1960)

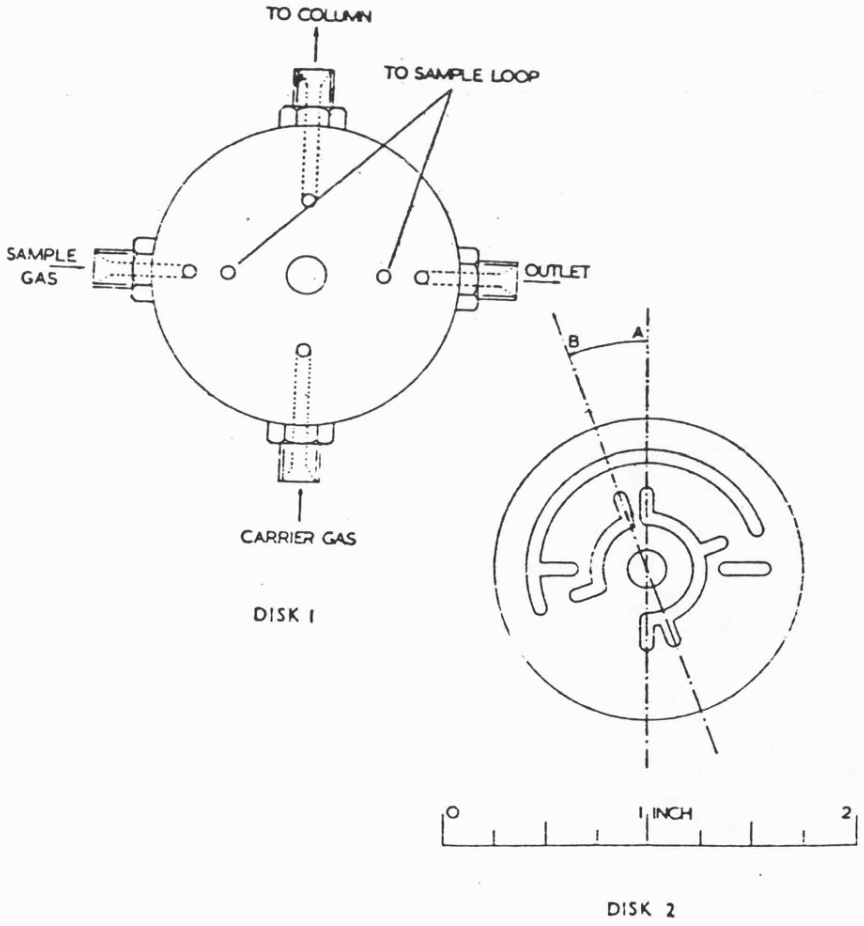


Fig 6.28
Automatic Gas Sampling Device

Figure 6.28 shows the slotted mobile disk and the fixed disk with ports for connecting the sample gas, carrier gas, sample loop, column and vent. It is based on a hand operated valve described by Timms,

Konrath and Chirnside (1958).

Repeated sample introduction into the carrier gas stream is achieved in the Hill Hook valve by moving the mobile disk to and fro through 20 °. This motion is produced by a complicated cam and ratchet system. Although this valve has this complexity it does not supply the carrier gas constantly to the column as in the ideal case.

Considering again the valve analogy for this type of valve and drawing a timing diagram of its operation as shown in Figure 6.29.

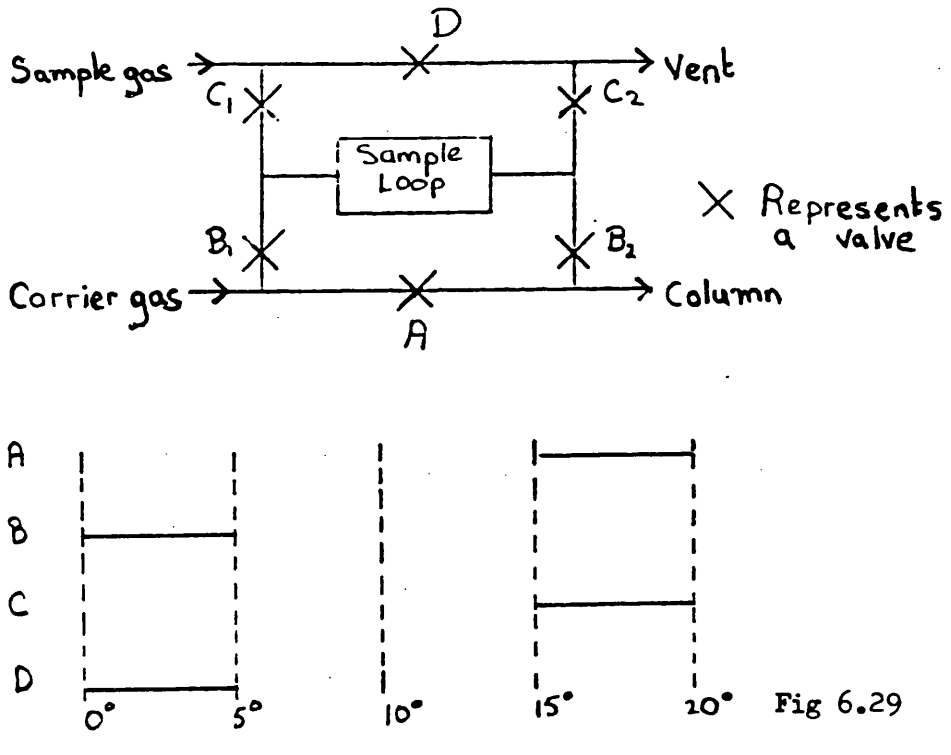
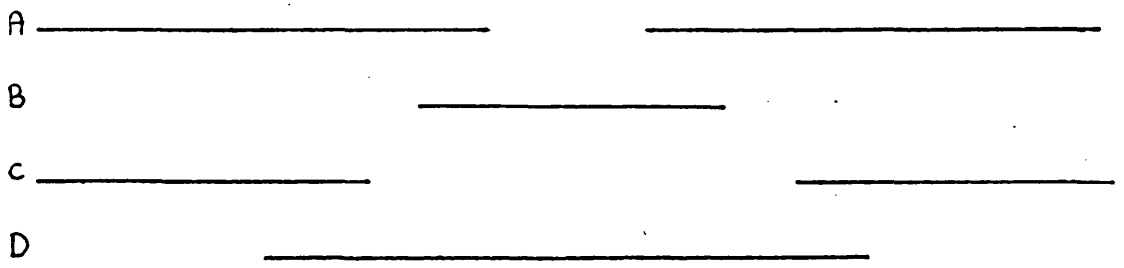


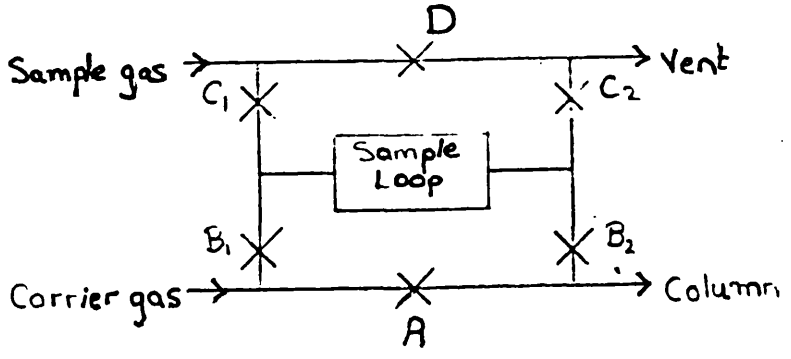
Fig 6.29
Timing Diagram for Automatic Device

There will be dwell at each end of the operational path. With this type of valve either there is a gap where everything is disconnected from each other, or the ports breach the gap which will cause all ports to be connected together causing sample wash out.

6.4.7 Improved Rotary Valve

The main reason for designing a different valve was to avoid the portion of the operational cycle where all ports are shut off at the same time. The timing sequence of operation of the 6 valves as shown in Figure 6.30 was worked out to give the desired characteristics.





× Represents a valve

Fig 6.30
Timing Programme for Improved Rotary Valve

Thus, at the initial position A is closed, B open, C closed and D open. This allows the carrier-gas to go directly to the column and the sample-gas to fill the sample-loop and go to the vent. D changes to be closed this connects the sample-gas to the vent in preparation for the sample loop being disconnected which happens when C opens. B then opens, but there is a restrictor in the line so sample is not yet injected. Only when A opens and the carrier is forced through the

sample loop is the sample injected. A closes, B opens, C closes and D opens in order. This resets the system ready for a further sample injection. If this scheme can be adopted, the sample will have been introduced into the carrier gas stream without the carrier ever being separated from the column.

It was found to be easier to make the valve give 4 injections per revolution. The space between one valve operating and the next was set at 5 ^{o} of arc, with a 10 ^{o} space between valve A opening and closing. Thus a timing diagram for the valve becomes:

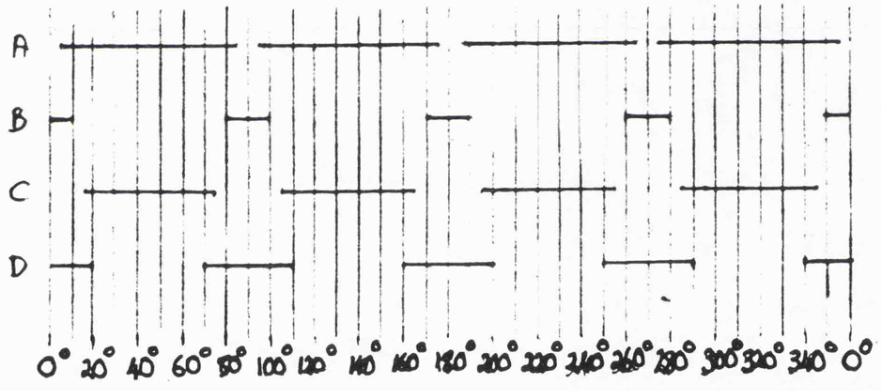
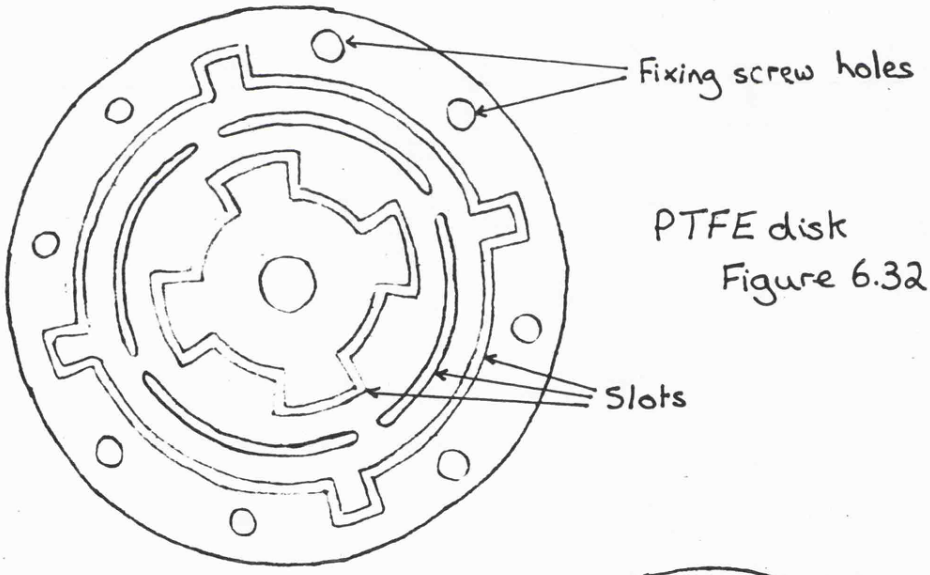
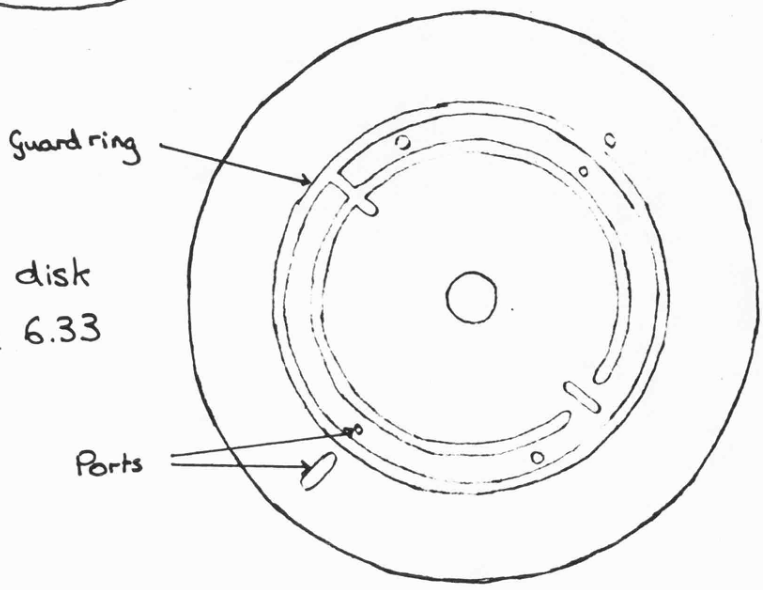


Fig 6.31
Timing Diagram for
4 cycle per
Revolution Valve

The moving disk in Figure 6.32 is made of PTFE which gives a low friction coefficient between itself and the steel stationary disk in Figure 6.33. The PTFE disk was machined to have the slots as shown. This pattern causes the connections and disconnections required for the valve to operate as shown in the timing diagram Figure 6.31. The stationary disk has the ports; 8 in all, 2 for each of the carrier gas and column connection and one each for each end of the sample-loop, the vent and the sample-gas. Two each are needed for the carrier gas and column to encorporate the restrictor which prevents the sample from being washed out while A is closed.



PTFE disk
Figure 6.32



Steel disk
Figure 6.33

It was found to be necessary to add the guard rings in the form of vented slots on the stationary disk. They were placed to come between the middle ring and the inner ring,and between the middle ring and the outer ring. Their purpose is to prevent carrier gas from flushing out the sample by crossing the gaps in the middle ring, and using this route to atmosphere. With the guard rings any carrier not following the correct path should be intercepted by the vented guard rings, and not go through the sample-loop to vent. In order that the pressure changes in the valve are kept to a minimum, it was decided to keep the outer ring at carrier gas supply pressure throughout the operation of the valve. This was achieved by cutting a slot in the stationary disk from the carrier gas port so that it would reach the outer parts of the outer ring during sample introduction. This ensures that the pressure gradients within the valve are kept as constant as possible.

The rotating disk was driven by a 6v Meccano motor through the motor's gear box and a worm drive. A very small amount of vasaline was applied to the steel disk to prevent it from rusting, which would otherwise occur, due to the water vapour in the patient's expirations.

Unfortunately the valve did not inject the same amount of sample on each of the 4 injections per revolution, although for a particular pressure it injected constant amounts for each position of the valve. That is, if the sample is introduced then the amount eluting for 0 ^{o} position say the 1st, 5th and 9th etc peaks will be the same, but the 1st and 2nd peaks will not be the same. This is shown on Figure 6.34.

Switching to a system where there is only one injection per revolution would ensure regularity of sample size as there would be only one phase.

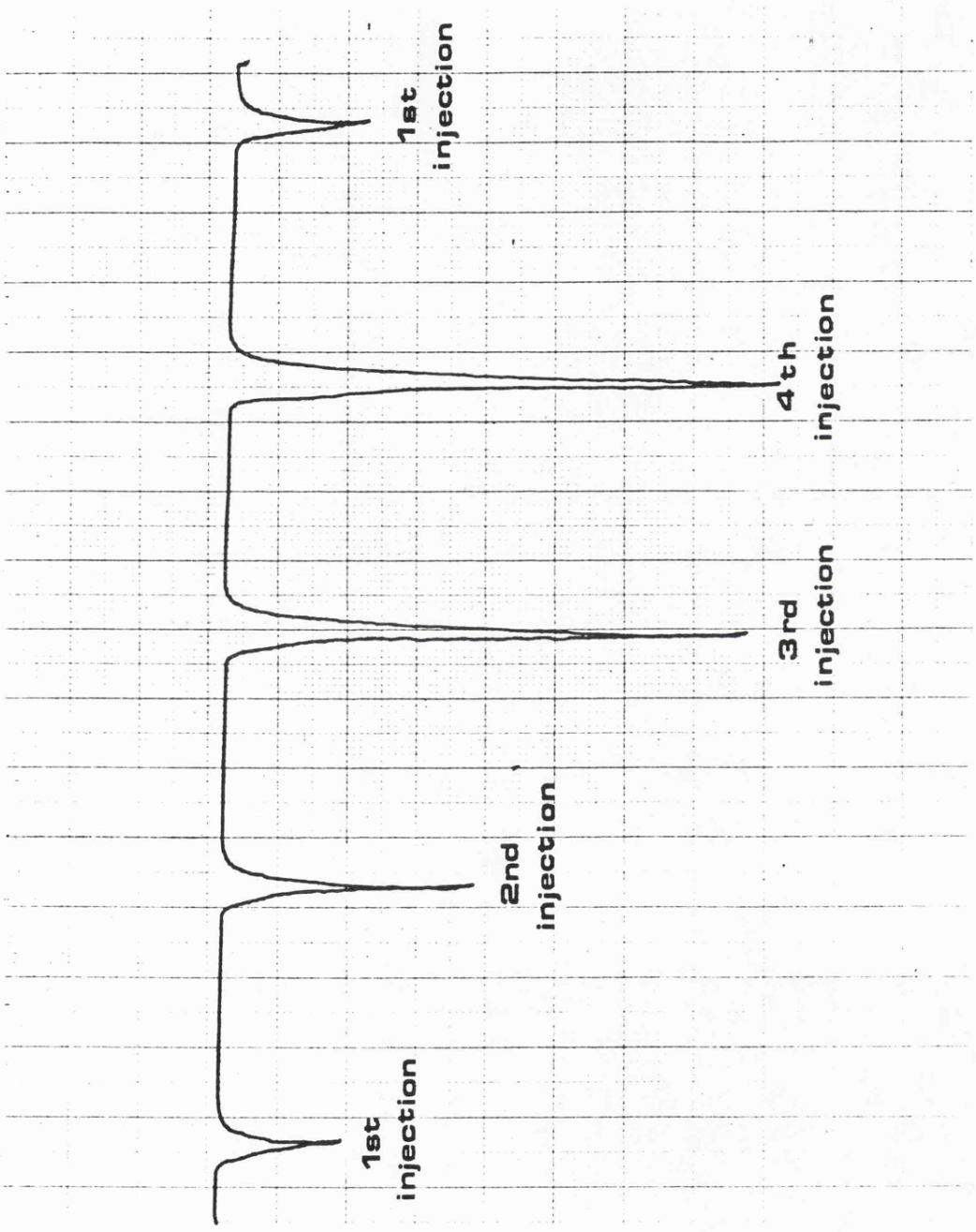


Fig 6.34 Showing result of repeated Injections by 4 Cycle Valve of Nitrous Oxide.

6.4.8 Single Shot Rotary Valve

A single shot rotary valve shown in Figure 6.36 was investigated, but even allowing for a modification in the ideal timing diagram the valve still requires one more level of slots than the 4 shot valve. The modified timing diagram is shown in Figure 6.35, which has a break in the sample gas filling about 180 °. The extra level of slots shown in Figure 6.35 would entail either cutting down on the space between slots, or increasing the size of the disks with the difficulty in ensuring flatness over the larger area. It was also felt that if sample was washed out in the 4 injection per revolution valve then it would be washed out in this valve too. Slight pressure changes could result in changes in the volume of sample injected, so this line of investigation was discontinued.

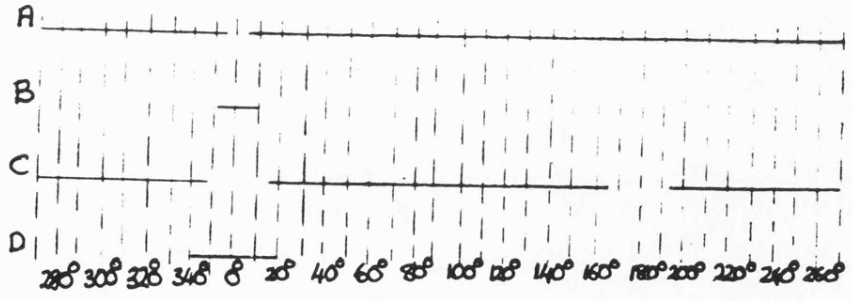


Fig 6.35

Timing Diagram for

Single Shot Valve

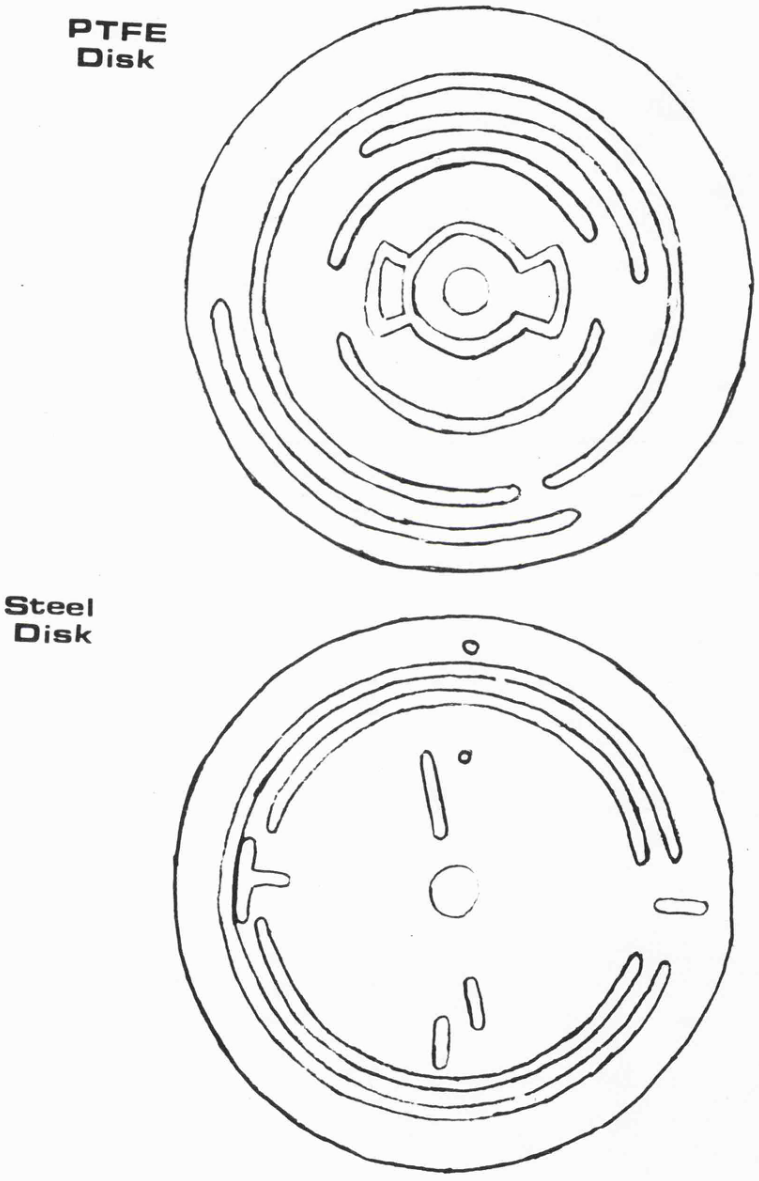


Fig 6.36

Single Shot Valve

6.4.9 Solenoid Operated Valves

By using solenoid operated valves, whose opening and closing could be controlled by logic, a very adaptable sample injection system could be developed. The logic would be programmed to achieve the desired timing sequence and the particular sample introduction rate could easily be varied.

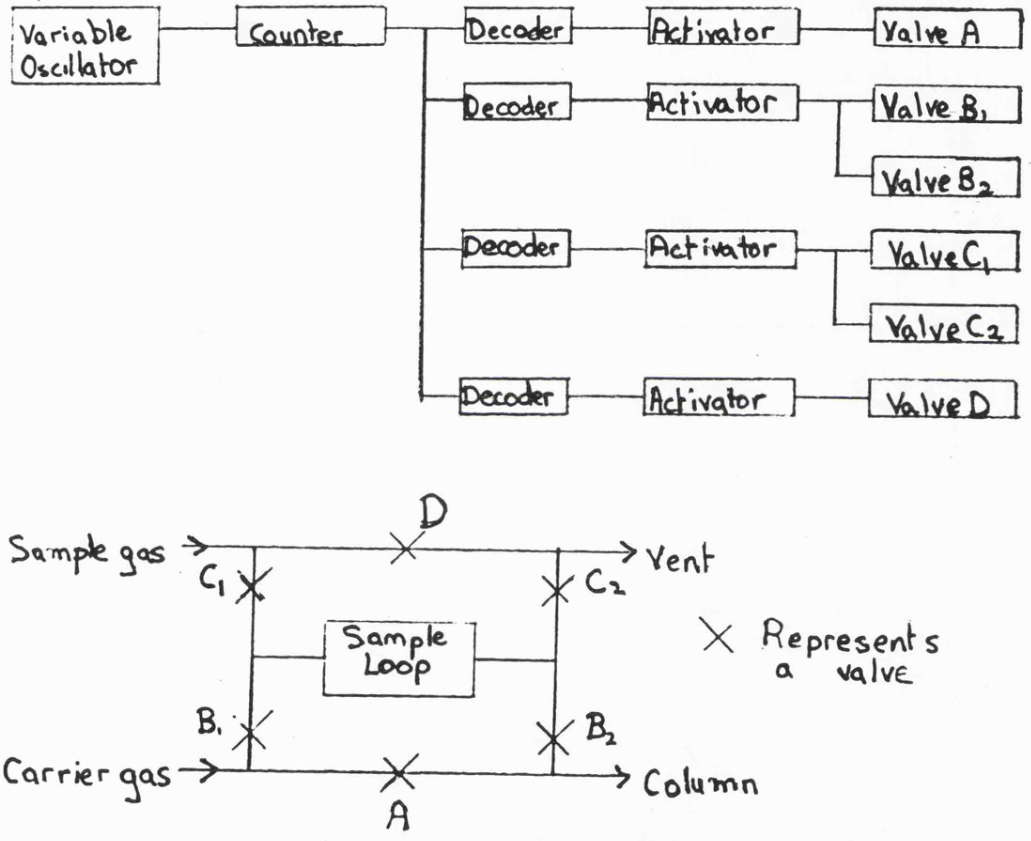


Fig 6.37

Thus the decoder for A would cause the activator to open when the counter reached a particular value and to remain open until another particular value was reached. Changing the rate of pulses fed to the counter would change the time for the whole cycle of gas sample injection.

The solenoid operated valve would need to have a very low dead volume to give satisfactory operation.

A prototype model was built using a bicycle valve and a reasonably low volume valve resulted although because the rubber seal of the bicycle valve which would swell and seal the valve this could not be used practically. However, by using a different seating material this scheme could prove satisfactory.

The outline of the required operation of a solenoid operated gas-sampling valve has been set out. Let us look at the practical aspects.

6.4.9.1 The Valve

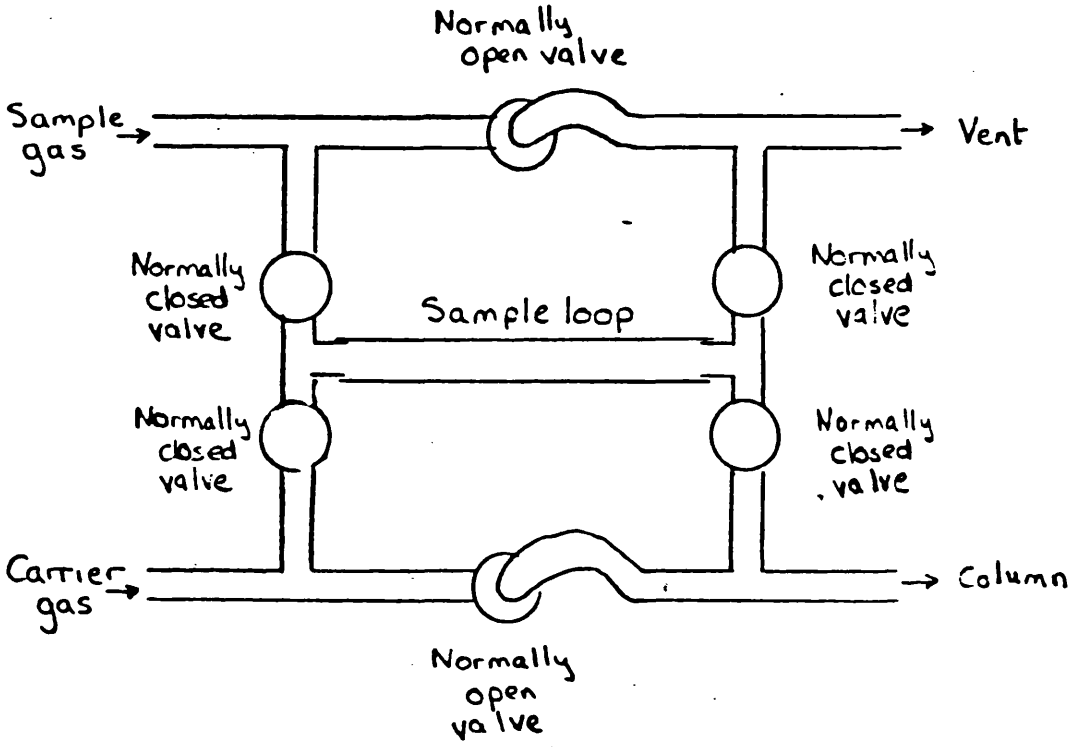
There is a need for a fast acting, low dead volume solenoid operated valve before the gas-sampling system can be built. This need is met by the Clippard Minimatic Valve which has a fast response (5 milliseconds) and a low dead volume; the only moving part travels 0.007". It does not need lubrication, is cold running and only requires a low voltage supply. The type chosen runs from a 12v dc supply. The valve is available in the normally open (NO) and the normally closed (NC) modes. It was decided to make use of both of these types.

6.4.9.2 Configuration of the Valves

Using a combination of normally open and normally closed valves as shown in Figure 6.38. With no power applied the sample-gas will pass through to the vent and the carrier gas is connected to the column, a safe position.

It is important that the sample volume should be limited to the volume of the loop as much as possible. This will ensure that the sample is efficiently flushed on to the column. The valves have a larger volume between the "out" port and the seal than between the "in" port and the seal. The volumes have been calculated at 0.14cc at the "in" port, and 0.25cc at the "out" port. There are 4 valves around the sample loop so these should be arranged so that the "in" ports are

together and the volume of the connecting pipes is as small as possible.



Note. The Minimatic normally closed has side connections while the normally open has one side connection the other is on the top.

Fig 6.38

6.4.9.3 Operation of the Sampling Valve

Initially the valves were operated from a 3 position toggle switch. We will call the 3 positions fill, centre and inject.

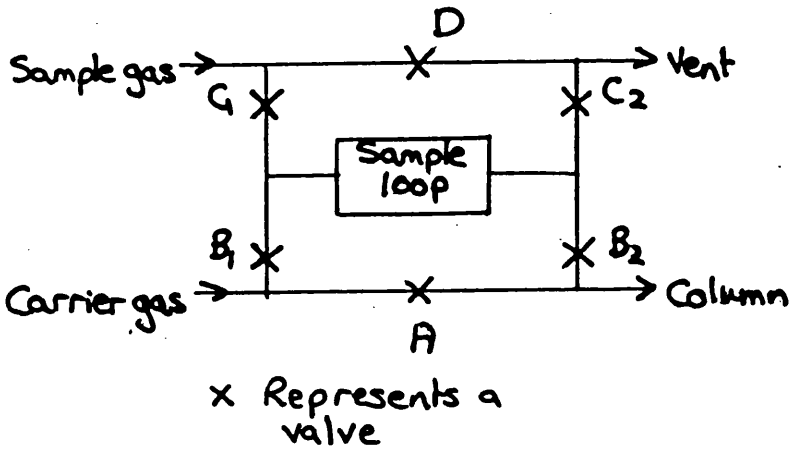


Fig 6.39

	Fill	Centre	Inject	Centre	Fill
D	C	O	O	O	C
C_1	O	C	C	C	O
C_2	O	C	C	C	O
B_1	C	C	O	C	C
B_2	C	C	O	C	C
A	O	O	C	O	O

Fig 6.40

Where C is closed and non-conducting and O is open and conducting gases.

It was decided to try the system initially with no overlap. It was felt that the fast response time of the valves would mean that the gas flows would be cut for a very short time and would not affect operation. This proved to be true.

As A and D are normally open, this means that D, C_1 and C_2 can be driven from the same waveform as they only need to be activated in the fill position. Similarly A, B_1 and B_2 may be driven together by

another waveform as they only need to be activated in the inject position.

So, when the switch is in the fill position D, C_1 and C_2 are activated; in the centre position none of the valves are activated and in the inject position A, B_1 and B_2 are activated.

This system proved satisfactory with the sample valve giving a repeatable injection. It was found that the length of dwell in the centre position had no effect on the injection so when the system was automated it was decided simply to drive the valves from a pulse and its inverse.

This pulse was produced from the timing circuit discussed below and amplified to drive the valves. The pulse width and repetition rate could be altered, the pulse width from 10 msec to 990 msec, and the repetition rate from 1 sec to 99 sec. This was to enable the optimum values to be determined.

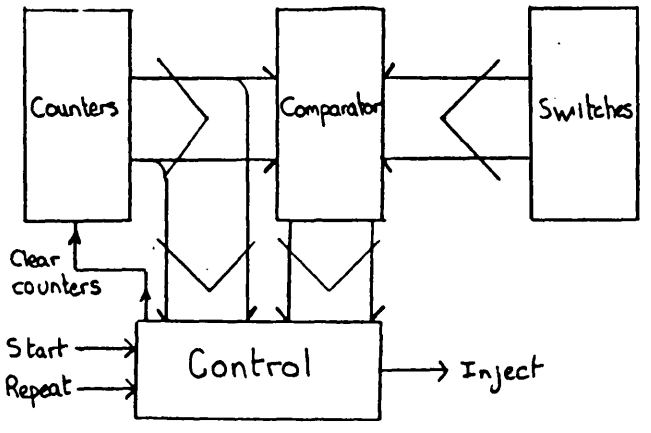
In the production meter this facility would not be needed as fixed values would be used. The circuit could then be simplified as discussed later.

6.4.9.4 Electronics associate with Solenoid Operate Valve

The electronics are shown in Figures 6.41, 6.42 and 6.43. TTL digital circuits have been used as they are easy to handle, readily available and the author is familiar with them. CMOS could be used instead if low power consumption was required.

The 555 timer provides a source of 100 Hz pulses. These are counted by a counter. The number set on the switches are compared with this count.

Initially the valves will be in the fill position;when the circuit is turned on the valves are switched to introduce the sample. They remain in this position until the number on the first 2 sets of switches


Counters
Comparator
Switches
Clear counters
Start
Repeat
Control
Inject

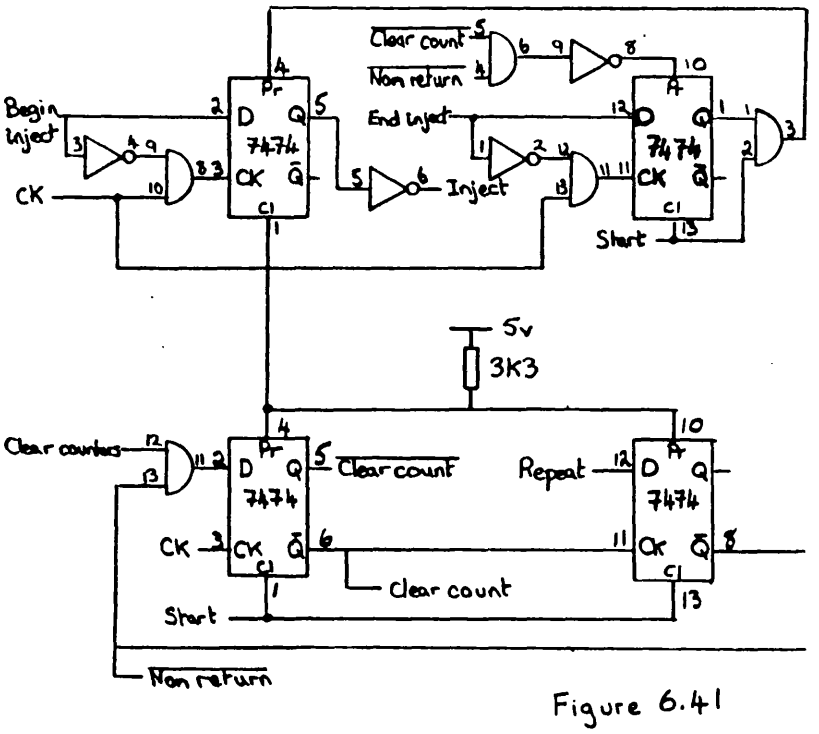
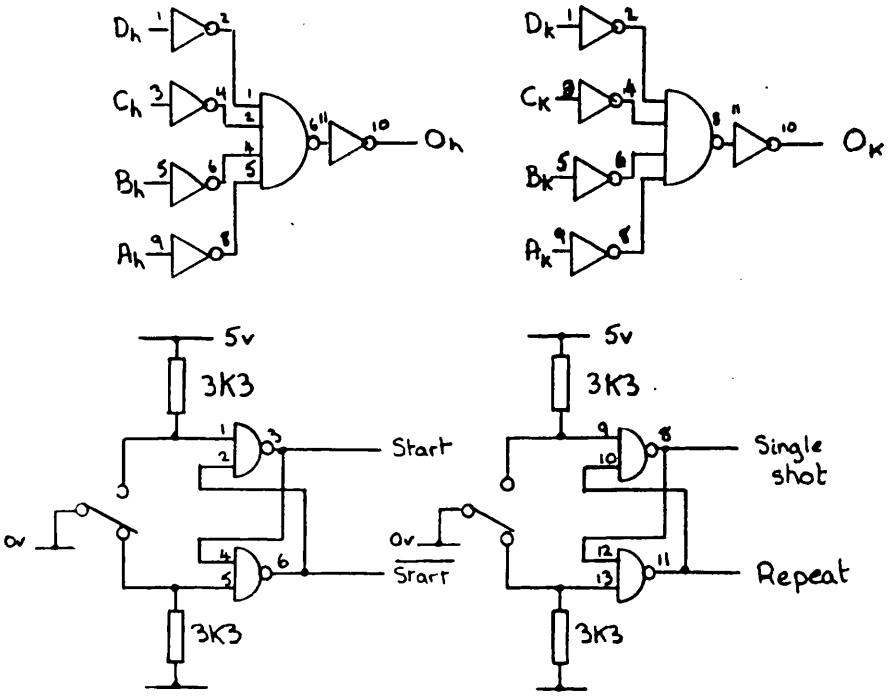
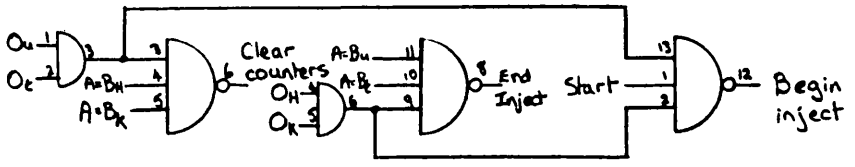

Clear count
Non return
Begin inject
End inject
CK
Inject
Start
5v
3K3
Clear counters
Clear count
Repeat
CK
Clear count
Start
Non return

Figure 6.41


Dh
Ch
Bh
Ah
Oh
DK
CK
BK
AK
OK
5v
3K3
Start
0v
Srart
Single shot
Repeat


Clear counters
End Inject
Start
Begin inject

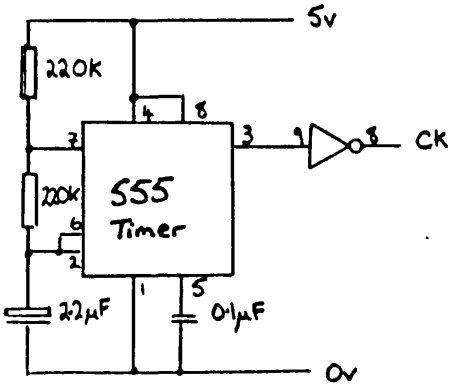
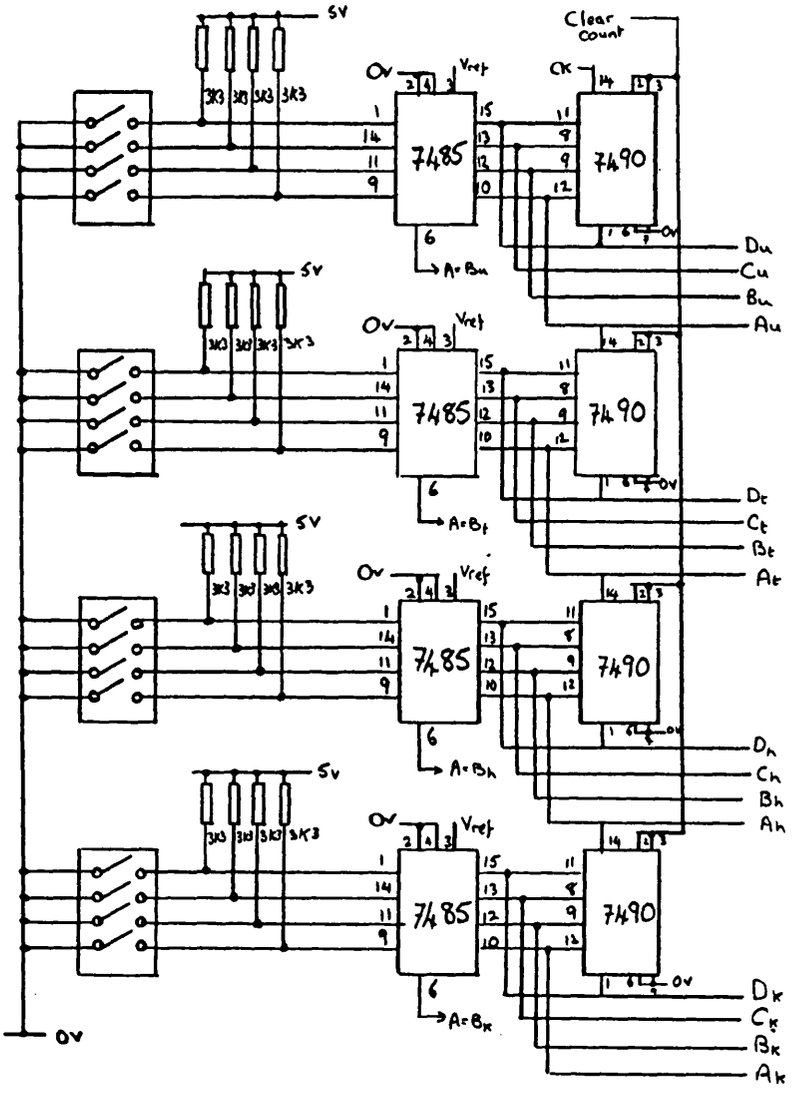

5v
220K
555 Timer
CK
0.1μF
0v

Figure 6.42


5V
3K3
Clear count
0V
Vref
CK
7485
7490
A=B
Du
Cu
Bu
Au
Dt
Ct
Bt
At
Dh
Ch
Bh
Ah
Dk
Ck
Bk
Ak

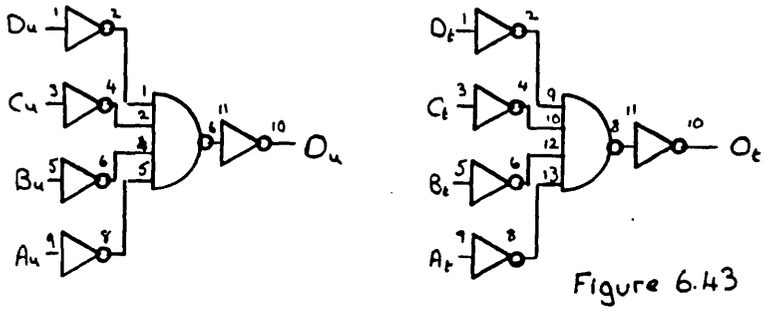

Du
Cu
Bu
Au
Ou
Ot
Ct
Bt
At

Figure 6.43

match the number on the first 2 counters. Then the valves are switched back into the fill position. If the repetative mode is selected then the counters will continue counting until the number on the second 2 sets of switches matches the number on the second 2 counters. Then the cycle will restart with an inject until the first number is matched; this is followed by a fill period until the cycle restarts. Switching to the off position clears the counters and the system is ready for the next inject cycle.

The output from this cycle is a TTL pulse which must be amplified before it can be used. A considerable current gain is required, and the circuit used is shown in Figure 6.44.

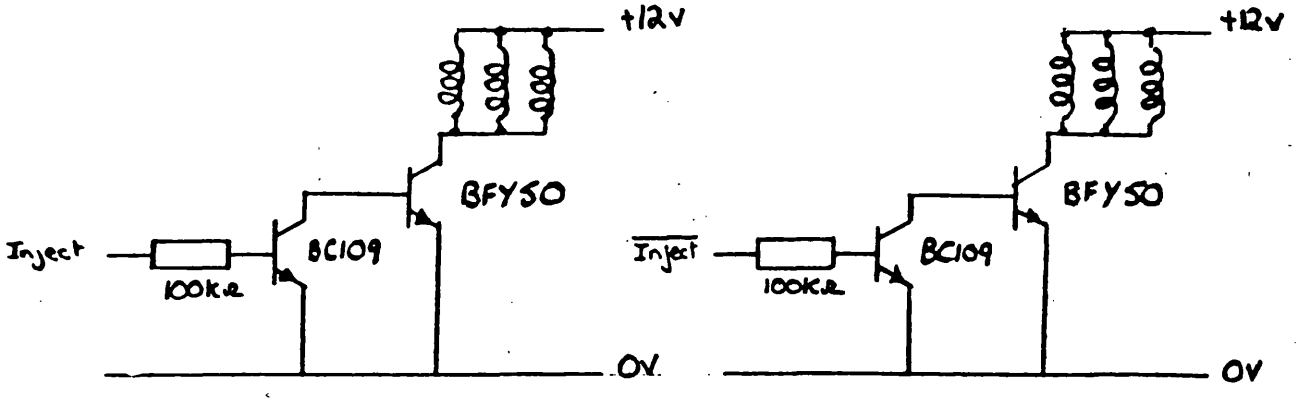


Fig 6.44

This set up produced a repeatable introduction of sample, the valves hold a pressure and with the carrier-gas flow-rate does not appear to be disturbed.

For a production model the only changes that would be required are slight alterations to the electronics as a fixed repetition rate and pulse width could be implimented with less devices. These changes will not affect the operation of the sampling valve which is perfectly satisfactory.

6.5 Gas Chromatographic System Employed

The system that was selected for further trials is described below.

6.5.1 Column

A 4 mm diameter glass column plugged at both ends with glass wool and filled with Chromosorb W NAW coated with 15% by weight Kel-F-Oil was selected. The columns were made up in 10cm, 15cm, 20 cm and 25cm lengths.

6.5.2 Carrier-Gas

Air from a gas cylinder was fed through a pressure reducing valve and used as the carrier gas. Air was chosen as it can be compressed from the atmosphere so that in the clinical instrument bottled gas can be avoided.

6.5.3 Gas Sampling Valve

A 6 solenoid-operated valve system electronically controlled was selected. The volume of the sample may be altered simply by changing the size of the sample loop.

6.5.4 Detector

A refractive index detector based on a Zeiss refractometer was used. Movement of the fringe pattern is detected by 2 photo cells and electronic processing of this gives a buffered signal of the difference in the photo cells output.

Chapter 7

7. Results

An experimental chromatograph was set up. The component parts were as described before, that is: a solenoid operated gas-sampling valve, various lengths of 4 mm internal diameter glass tube filled with Chromasorb W NAW coated with 15% by weight Kel-F-Oil and a refracture index detector.

Having chosen the column materials and the carrier-gas the variables which remain to be chosen are the column length, the carrier-gas flow-rate, the sample volume and the temperature of operation. An excessively large sample would increase the width of the peaks. The temperature, column length and flow-rate will affect the separation as well as the shape of the peaks.

7.1 Separation

A satisfactory separation will have been achieved if the sample is eluted in less than 15 seconds, and the peak for the anaesthetic is distinct from the peak for the other gases. The trace should ideally return to the base line between the 2 peaks. The requirements are illustrated in figure 7.1.

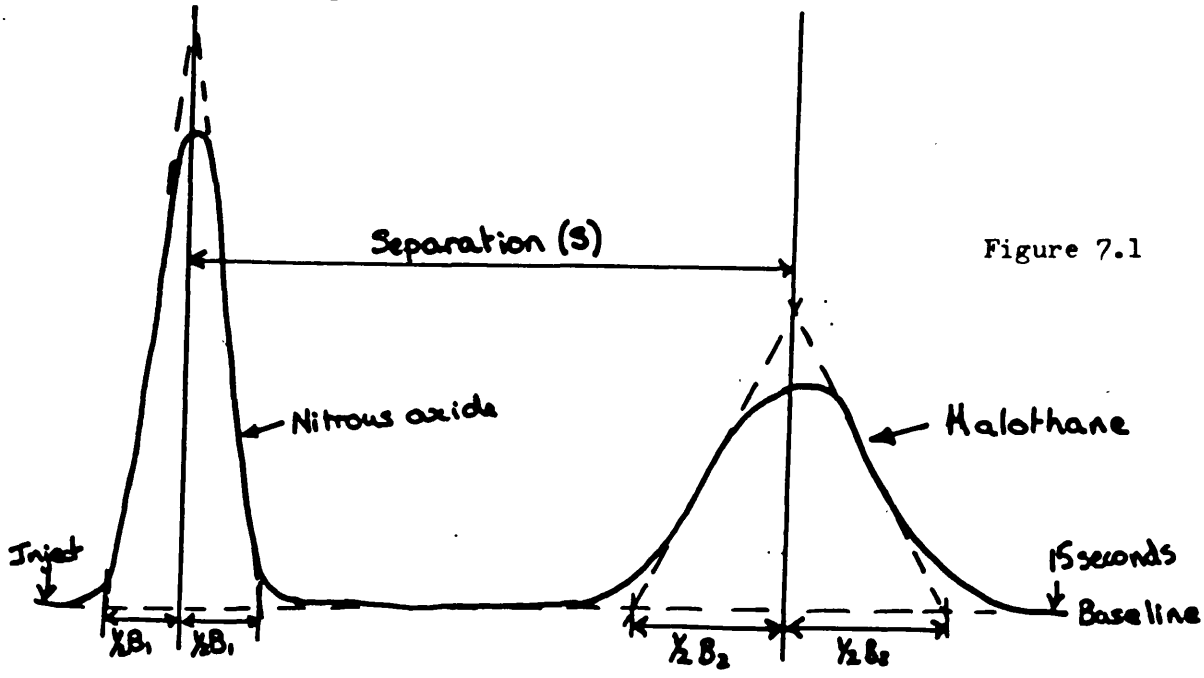


Figure 7.1

Assuming that the peaks are Gausian and thus symetrical about their maxima, and the separation between the peaks and the base widths are measured in seconds, then for the elution to be completed in 15 seconds requires that:-

$$\tfrac{1}{2}B_1 + S + \tfrac{1}{2}B_2 < 15 \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots 29$$

For the separation to be reasonable then

$$\tfrac{1}{2}B_1 + \tfrac{1}{2}B_2 < S \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots 30$$

These will be used as guides to determine the suitability of columns. Although if we require a return to base line between peaks we will need a more stringent requirement than the inequality 30.

7.2 Effect of Column Length

As a starting point 4 lengths of column were arbitraily selected. The column lengths chosen were 10 cm, 15 cm, 20 cm and 25 cm. For each length, operated at 19.2 ^{o}C, traces of the separation of nitrous oxide from halothane at carrier-gas flow-rates between 500 ml/min and 2,000 ml/min were taken. The base widths for both peaks were measured together with the peak separation.

The peak separation against the carrier-gas flow-rate is shown in Figure 7.2. As can be seen from the Figure, a particular separation will require a higher flow-rate as the column length increases.

Figure 7.3 shows a plot of the peak separation against half the sum of the base widths. The high flow-rates are nearest the origin. The 2 shaded lines indicate the points excluded by the inequalities 29 and 30.

It can be seen from this Figure that better separations are achieved with longer columns. The 10 cm column at this temperature is incapable of giving a satisfactory separation, while the 15 cm column is only just satisfactory over a narrow range of carrier-gas flow-rates.

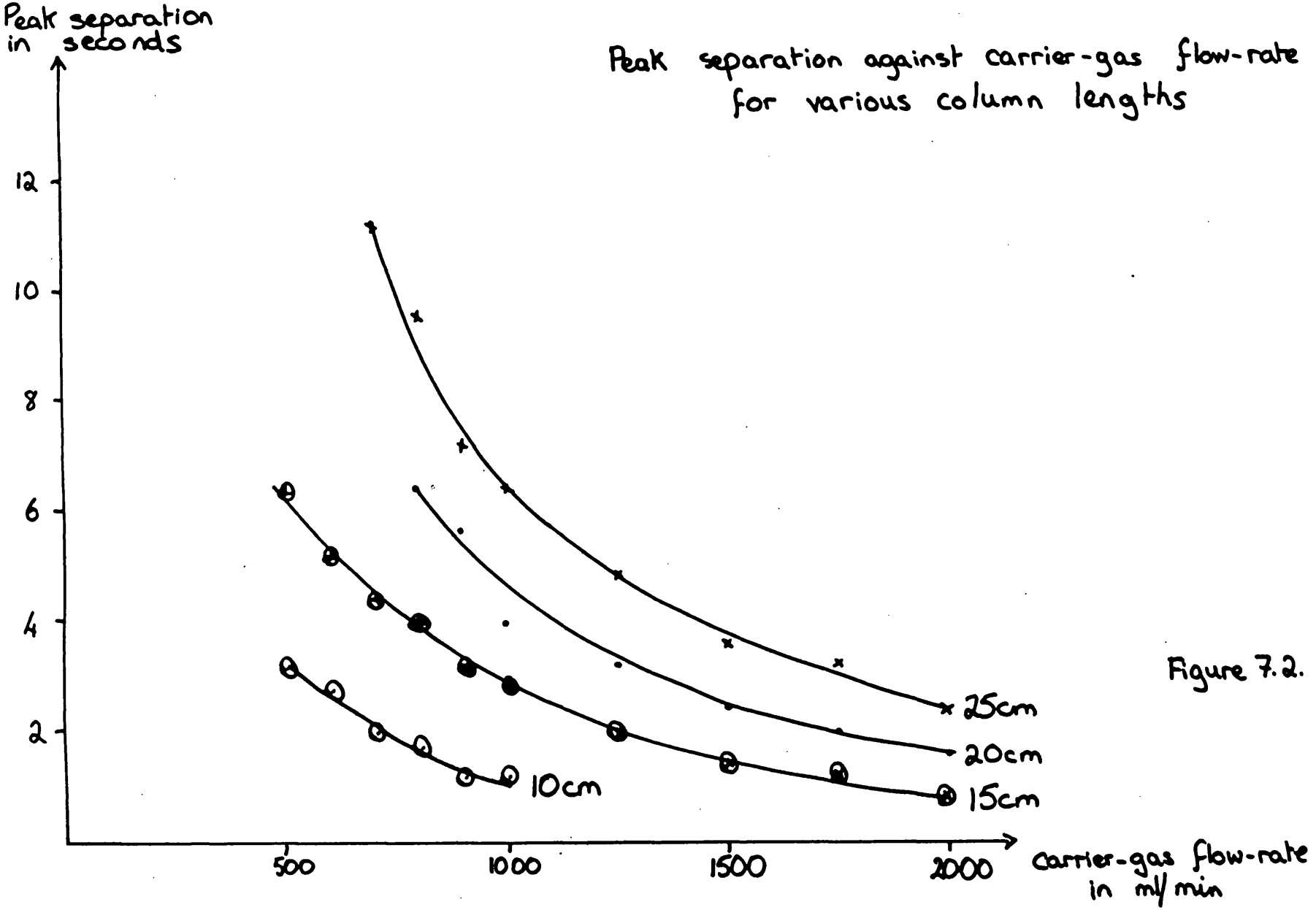
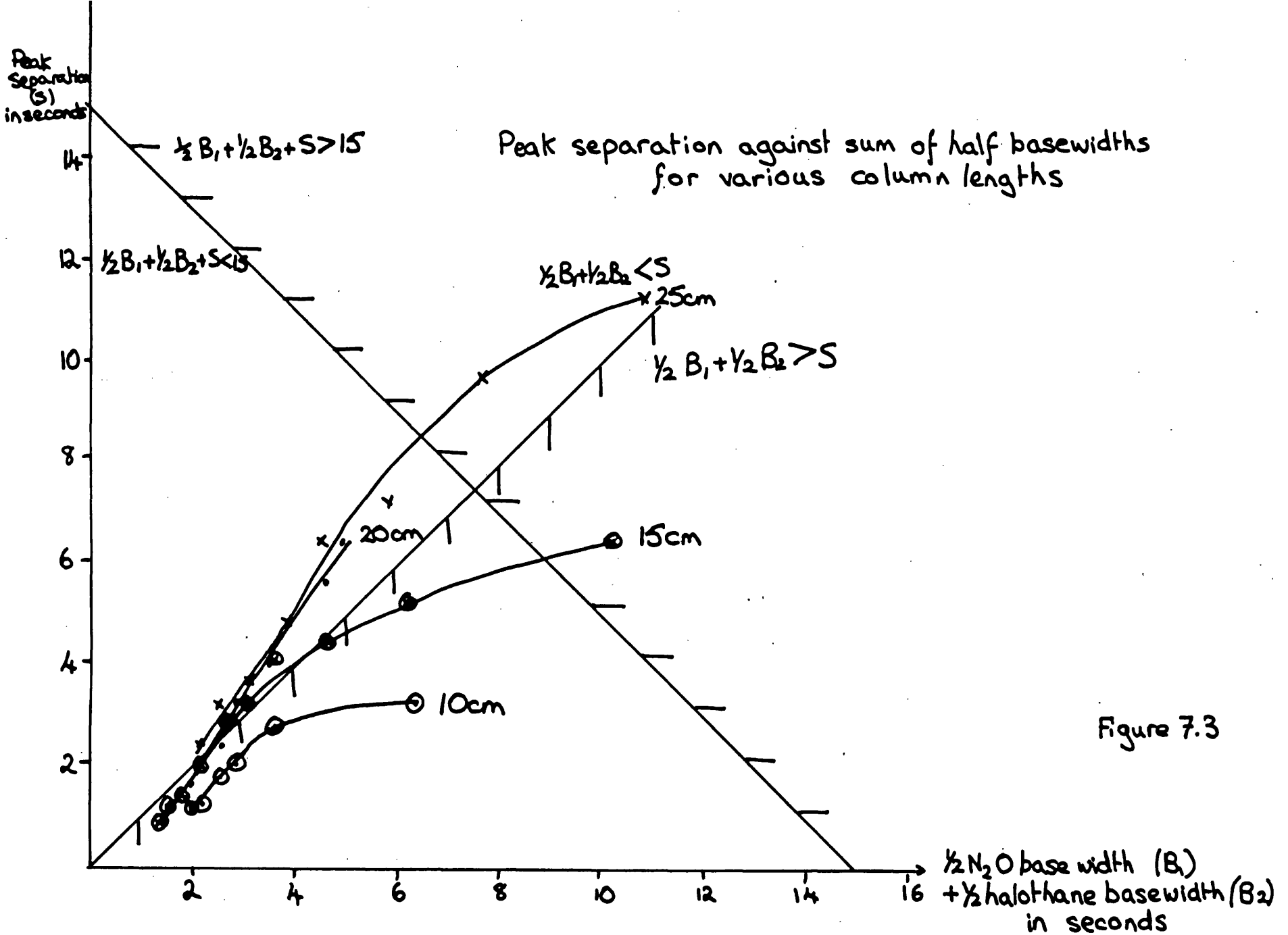

Peak separation in seconds
Peak separation against carrier-gas flow-rate for various column lengths
12
10
8
6
4
2
25cm
20cm
15cm
10cm
500
1000
1500
2000
carrier-gas flow-rate in ml/min

Figure 7.2.



Peak separation against sum of half basewidths for various column lengths

Figure 7.3

7.3 Effect of Temperature

From Figures 7.4 and 7.5 it can be seen that the effect of the carrier-gas temperature on the peak separation and base width over the temperature range illustrated is negligible. This is probably due to the low thermal capacity of the gas. The temperature of the column affects both the separation and base width.

Figure 7.6 shows the peak separation against half the sum of the base widths of the 2 peaks. As the temperature increases the separation improves. As previously stated we will be limited in this application to about 30 ^{o}C in order to avoid causing an explosion hazard.

7.4 Improving the Separation

Having had a brief examination of the system we can now propose ways of getting a satisfactory separation.

It has been shown that high temperatures improve the separation, so the column should be operated at as high a temperature as practical, in our case 30 ^{o}C.

Longer columns improve the separation at the expense of high carrier-gas flow-rates.

7.5 Ageing of the Column

A comparison was made of the effect on the separation of the column when it was newly filled with fresh column material, and the same column after 2 years of intermittent use. It was found that when new the separation of the peaks took longer than with the used column. This is illustrated in Figure 7.7.

A further investigation was carried out to compare the effects of storing the column material. Three 20 cm columns were prepared. The first contained the used material and is referred to as the old column.

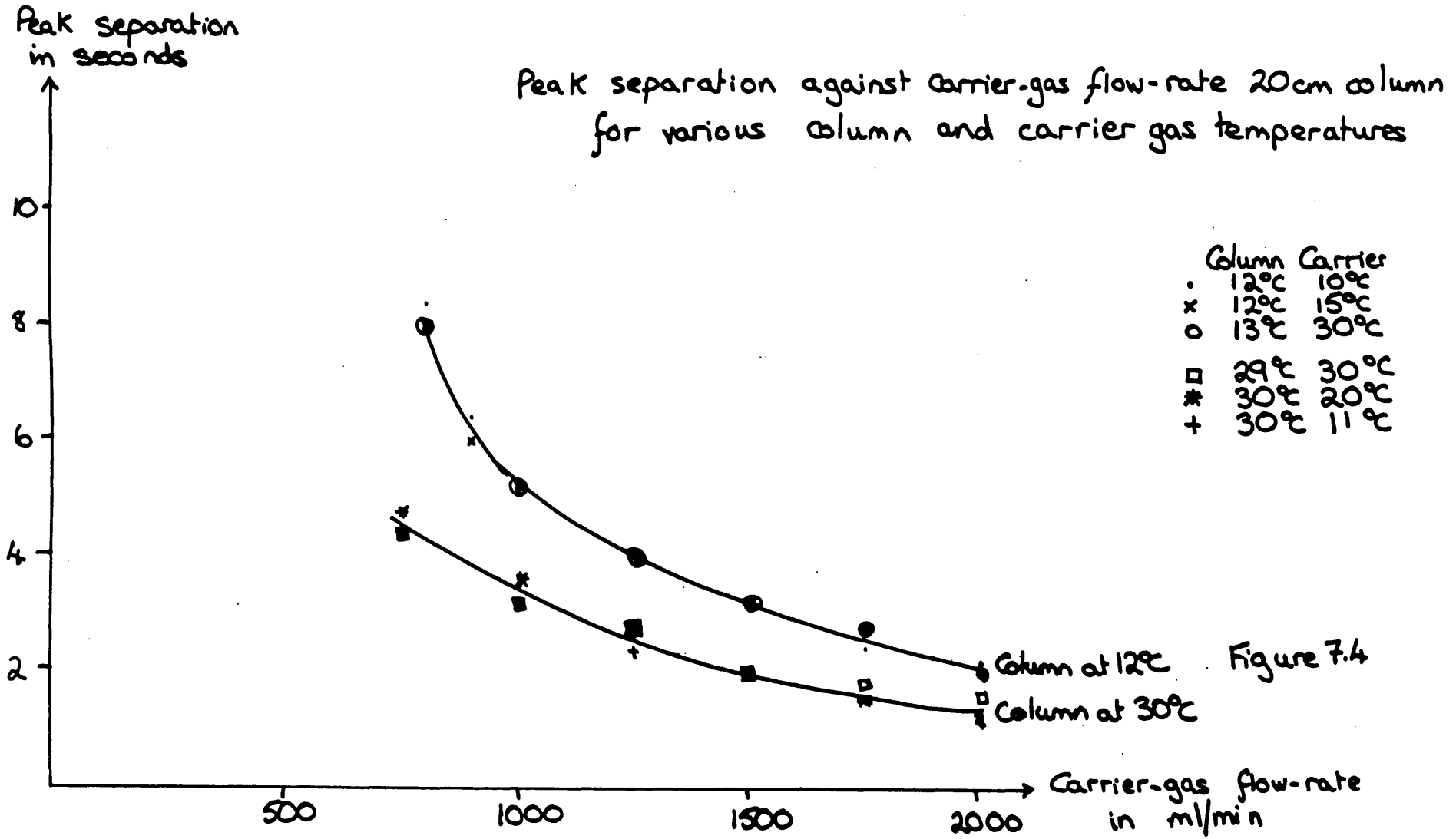

Peak separation in seconds
Peak separation against carrier-gas flow-rate 20cm column for various column and carrier gas temperatures
Column Carrier
. 12°C 10°C
× 12°C 15°C
o 13°C 30°C
□ 29°C 30°C
* 30°C 20°C
+ 30°C 11°C
10
8
6
4
2
Column at 12°C
Column at 30°C
500
1000
1500
2000
Carrier-gas flow-rate in ml/min

Figure 7.4

Halothane peak base width in seconds

Halothane peak base width against carrier-gas flow-rate 20cm column for various column and carrier gas temperatures

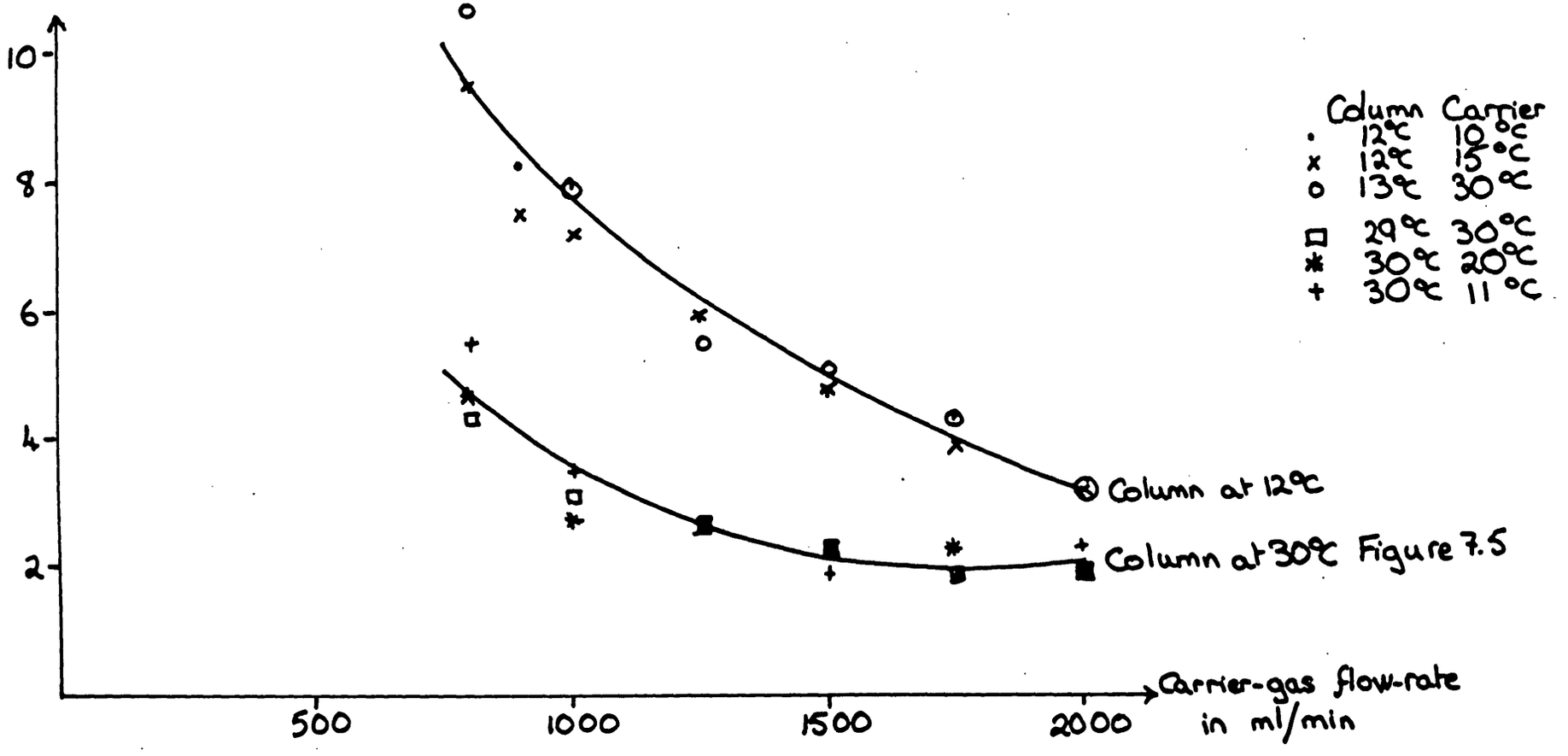
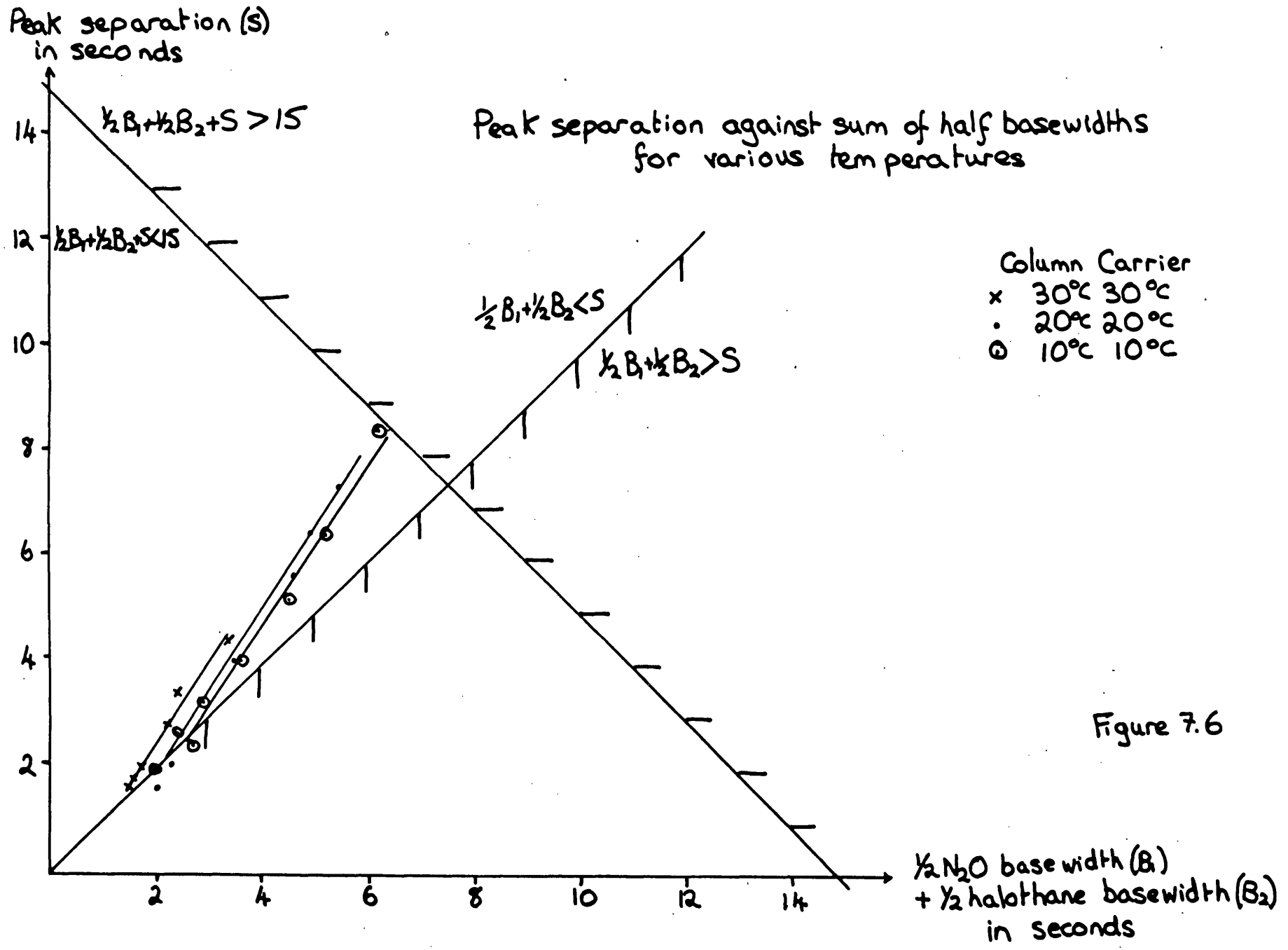


Figure 7.5



Peak separation against sum of half basewidths for various temperatures

Column Carrier
× 30°C 30°C
• 20°C 20°C
⊙ 10°C 10°C

Figure 7.6

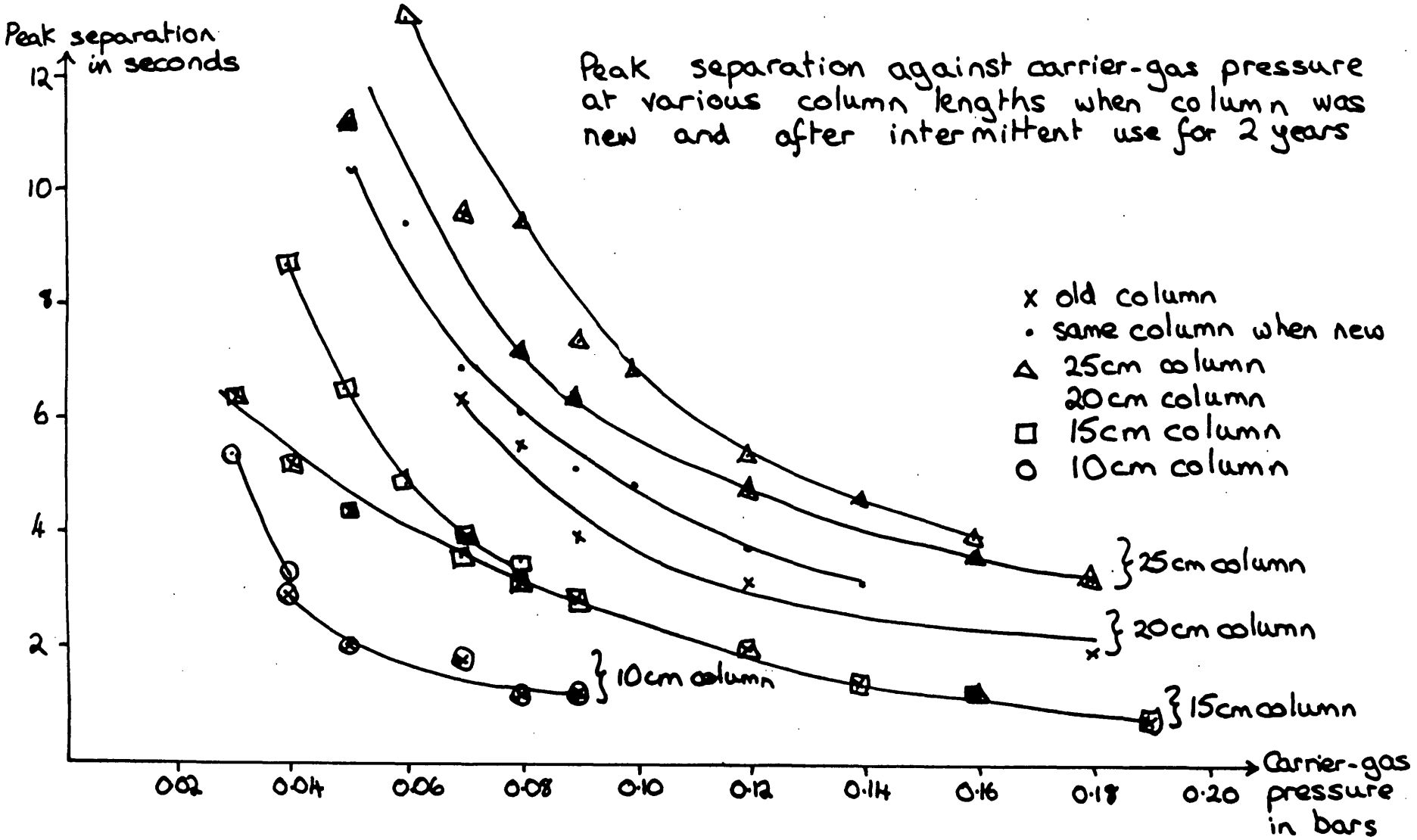

Peak separation in seconds
12
10
8
6
4
2
Peak separation against carrier-gas pressure at various column lengths when column was new and after intermittent use for 2 years
x old column
• same column when new
△ 25cm column
20cm column
□ 15cm column
○ 10cm column
25cm column
20cm column
15cm column
10cm column
0·02
0·04
0·06
0·08
0·10
0·12
0·14
0·16
0·18
0·20
Carrier-gas pressure in bars

Figure 7.7

The second contained material that had been stored in a screw topped container, but which had never been used; this will be referred to as the stored column. Freshly prepared column material was used for the third column and is referred to as the new column.

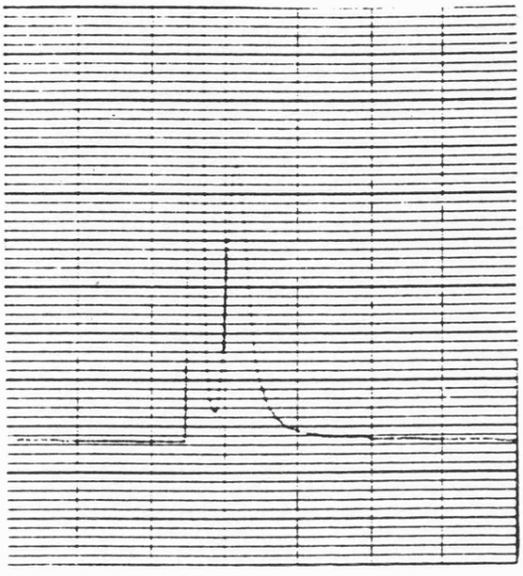
The 3 columns were run on the system. All other variables were held constant, the carrier-gas flow-rate at 1000 ml/min. Figure 7.8 shows the traces obtained. The old, stored and new columns results are shown in 7.8a, 7.8b and 7.8c respectively. Figure 7.8d shows the traces overlaid for comparison.

At this carrier-gas flow-rate there appears to be no difference between the stored and new material. The old column's trace for halothane appears quicker than the rest, but takes almost as long to return to the base line. This is probably due to the liquid phase having bled away resulting in less coating for the halothane to be absorbed by allowing an overall faster passage through the column. In some places the liquid phase will have left uncoated support particles which will slow the passage of some of the molecules of halothane and result in the peak trailing observed.

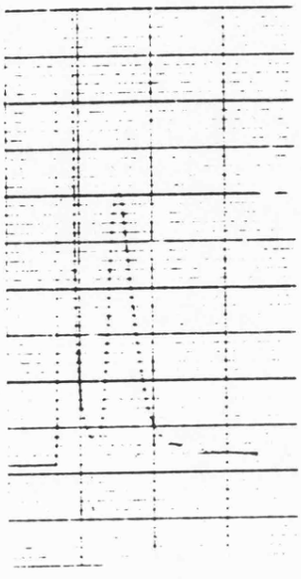
As a result of the effect noticed with the old column it was decided to use a much longer column which would allow a return to zero over a longer column life.

The results using 3 40 cm columns at a carrier-gas flow-rate of 2000 ml/min is shown in Fugure 7.9, again Figure 7.9d shows the 3 traces overlaid. The old and stored columns have very similar shapes, the old column having a greater trailing edge and thus a slower return to the base-line. The new column halothane peak is the last to appear.

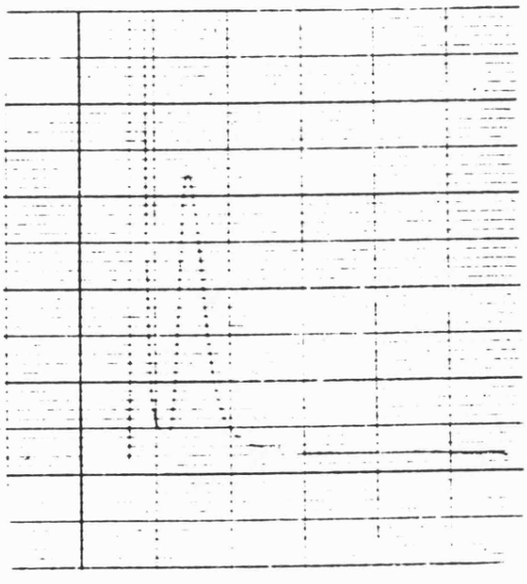
At this flow-rate a sample introduction every 15 sec may be achieved without fear of the air peak coinciding with the halothane peak.



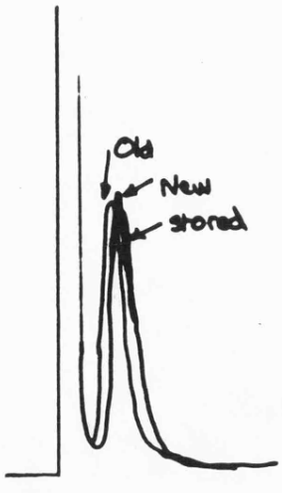
20 cm column old
Figure 7.8a



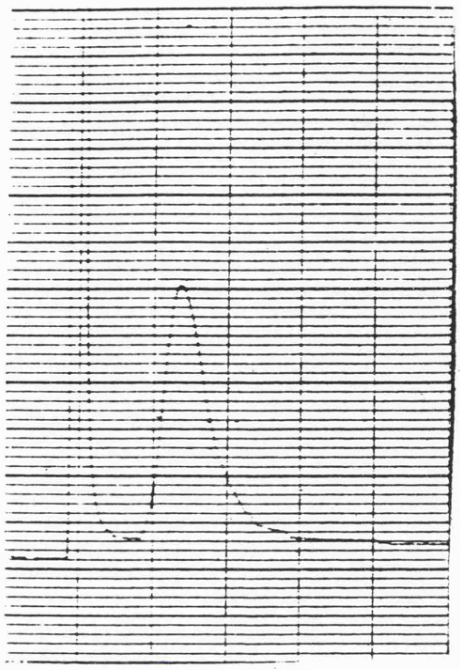
20 cm column stored
Figure 7.8b



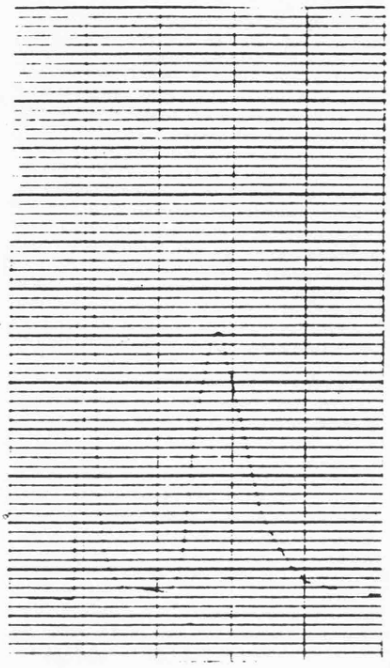
20 cm column new
Figure 7.8c



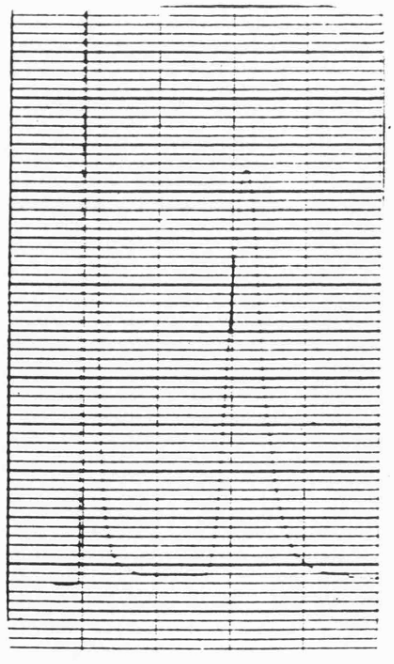
Traces overlaid
Figure 7.8d



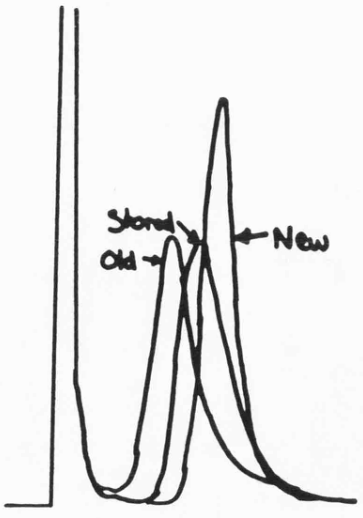
40cm column old
Figure 7.9 a



40cm column stored
Figure 7.9b



40cm column new
Figure 7.9c



Traces over laid
Figure 7.9d

7.6 Effect of Sample Volume

Using sample volumes from 0.2 ml increasing in 0.1 ml steps to 0.7 ml the peak height for each volume was measured. The column was 35 cm long, operated at 30 ^{o}C, with a carrier-gas flow-rate of 2000 ml/min.

The sample was composed of approximately 97% nitrous oxide and 3% halothane. It can be seen that the peak height against the sample loop volume is linear, the response doubling when the volume doubles. There was no detectable increase in the base width caused by the increased sample volume. At the flow-rate chosen the 0.7 ml sample will be washed out of the loop in 21 m sec which is small compared with the base width.

We shall choose to use a sample loop volume of 0.4 ml because the linearity has been demonstrated above this volume, and at higher sample volumes the effect of the baseline drift on the larger response will be lessened.

The way in which the sample loop was connected made it difficult to use sample volumes greater than 0.7 ml. However, the apparatus could easily be adapted to take larger sample loops if it proved necessary.

7.7 Separations Achieved

Halothane was separated from oxygen, carbon dioxide and nitrous oxide and a mixture of oxygen, carbon dioxide and nitrous oxide as shown in Figures 7.11 - 7.14 respectively. The oxygen peak occurs in the opposite direction to the others as oxygen has a refractive index less than the carrier-gas, while all the other gases have refractive indices greater than the carrier. The other first peaks all fold over indicating that the change in refractive index was so great that more than one fringe passed the photocells. Because the amplitude

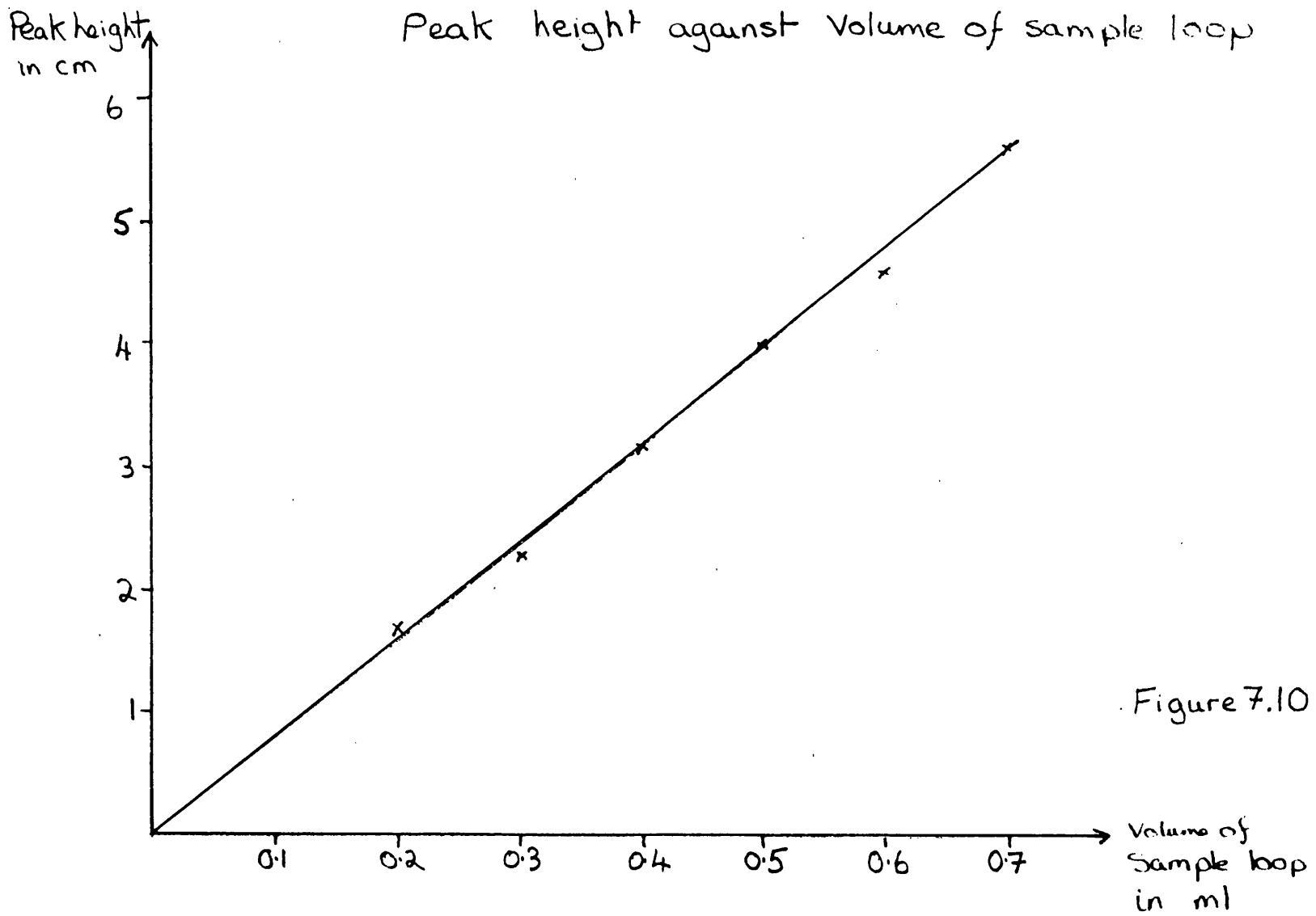

Peak height against Volume of sample loop
Peak height in cm
6
5
4
3
2
1
0·1
0·2
0·3
0·4
0·5
0·6
0·7
Volume of Sample loop in ml

Figure 7.10

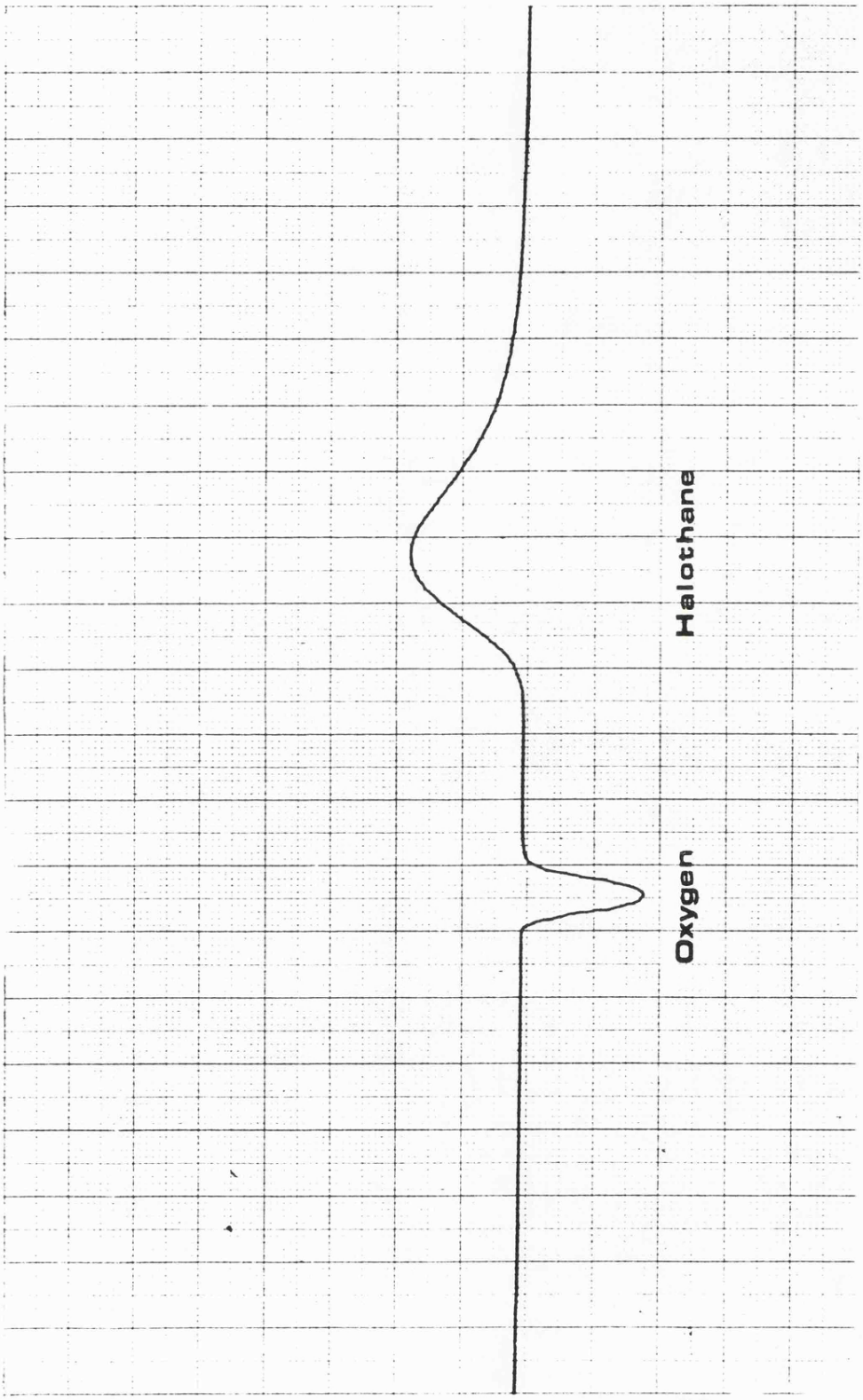


Figure 7.11

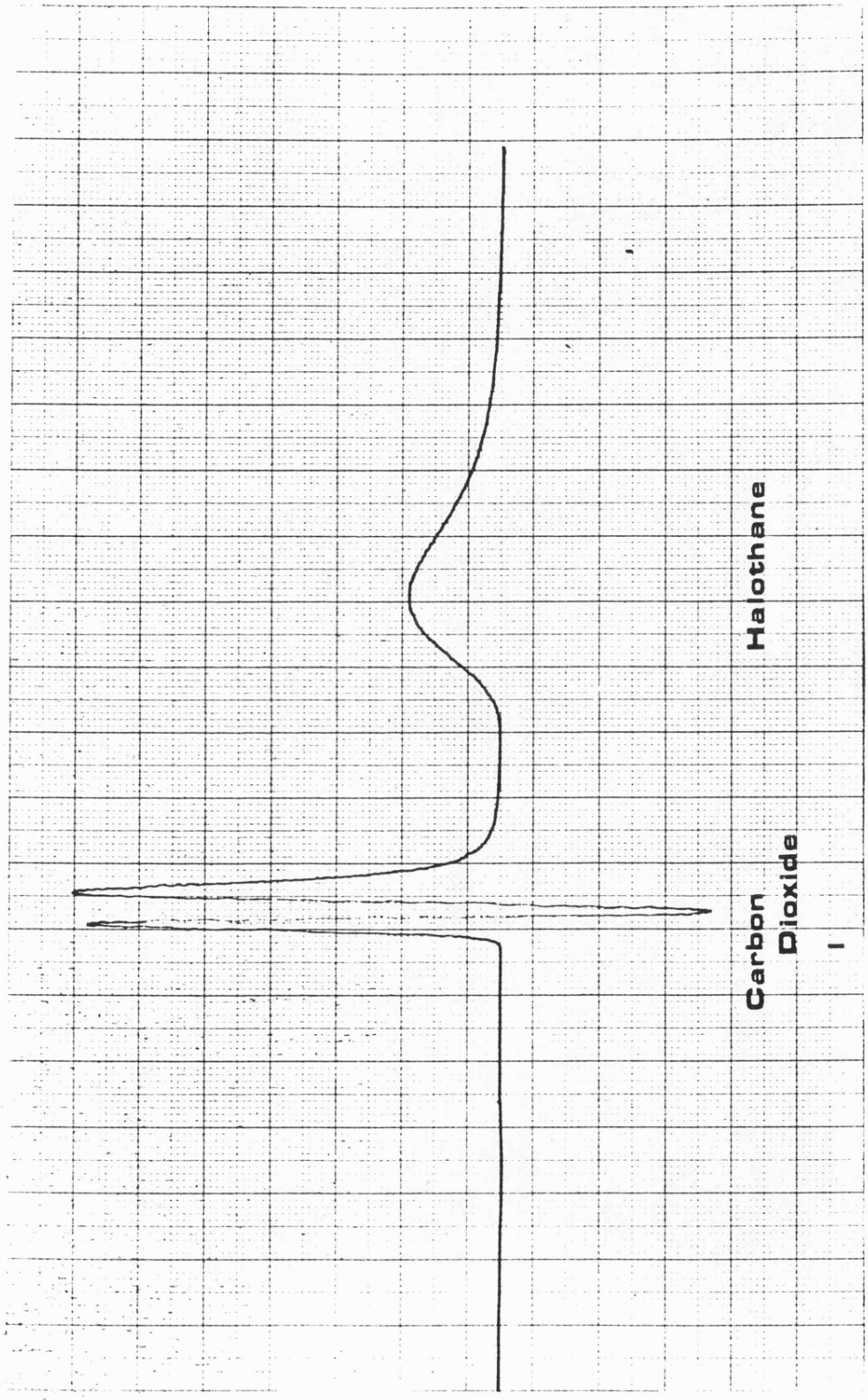


Figure 7.12

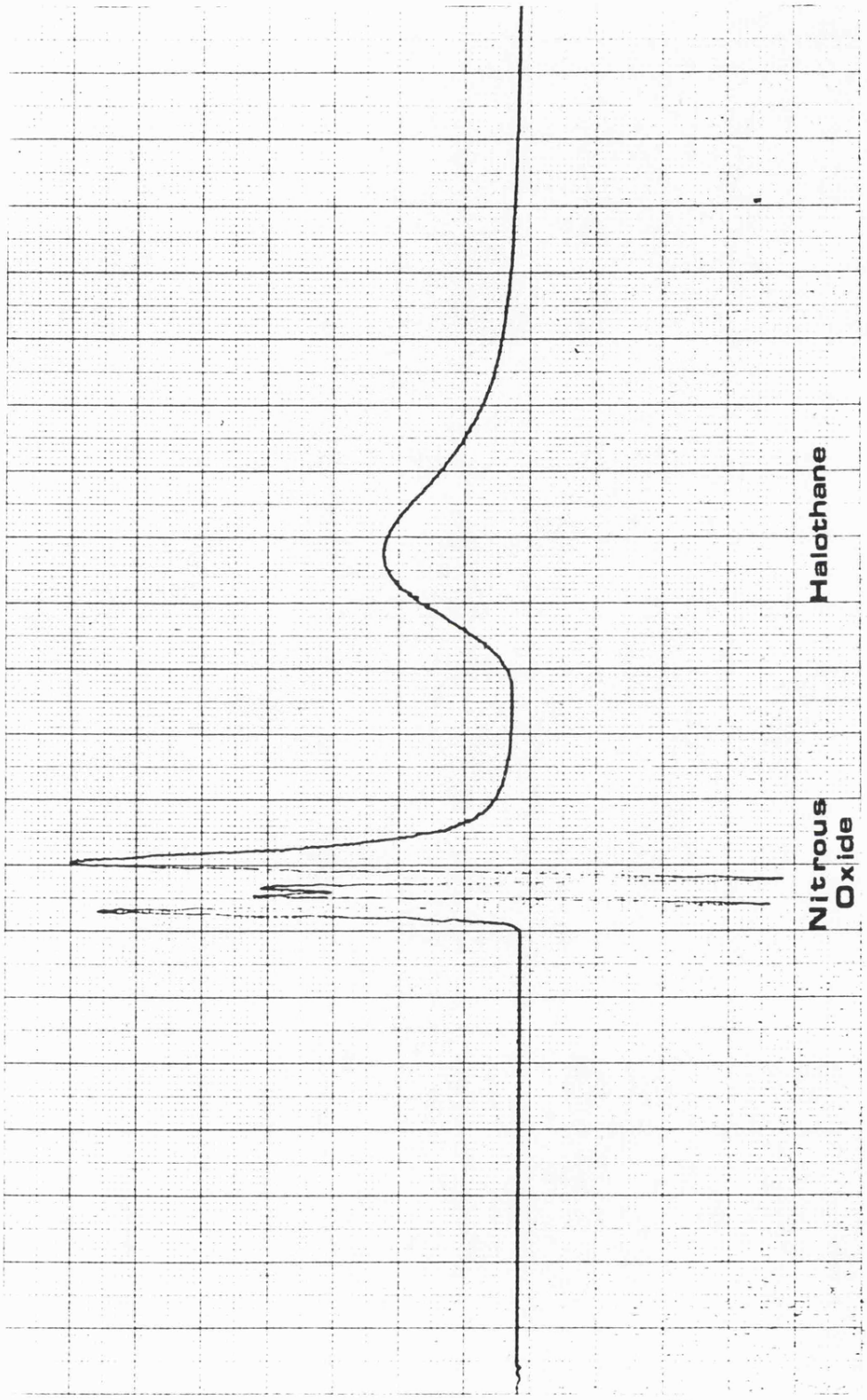


Figure 7.13

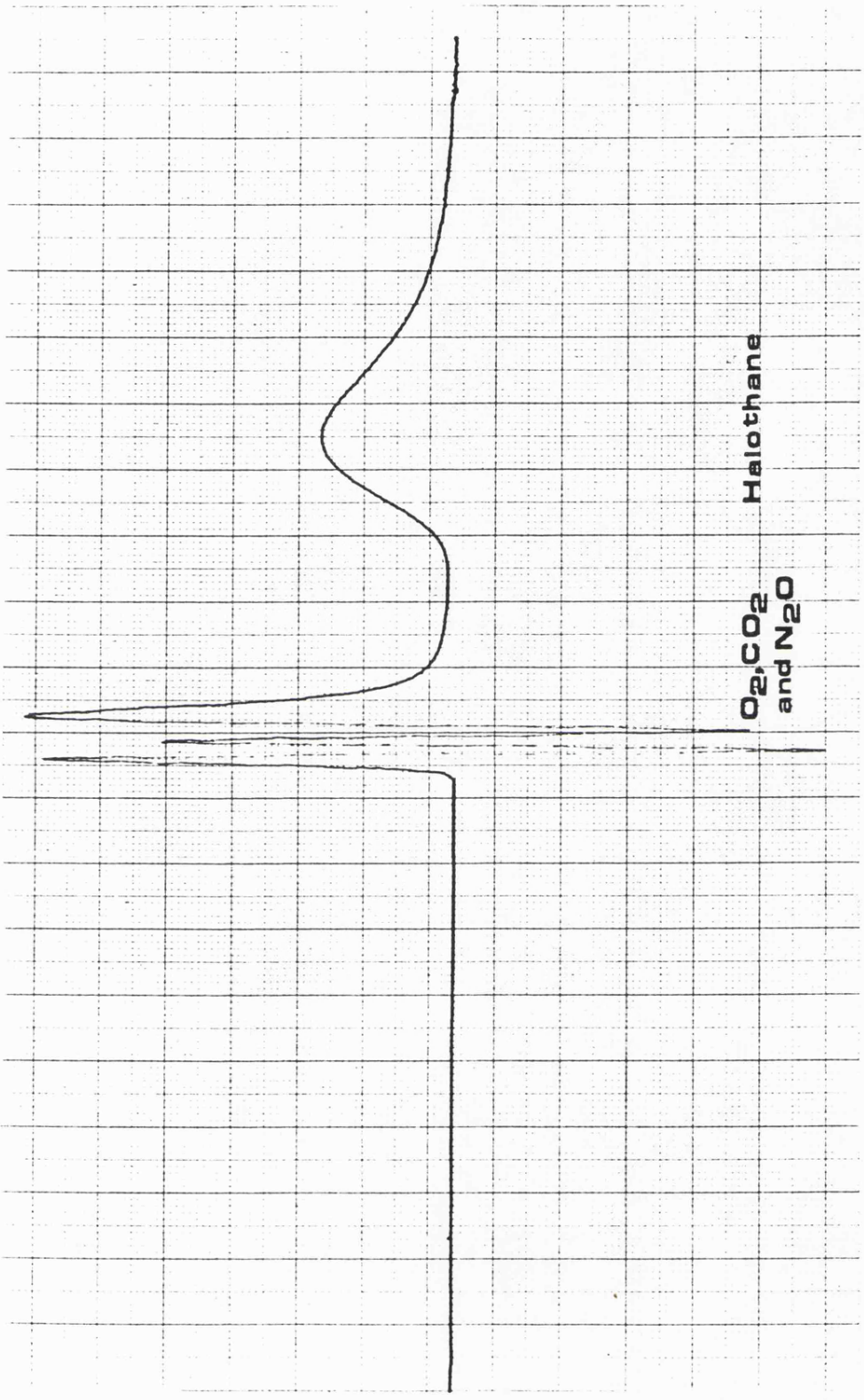


Figure 7.14

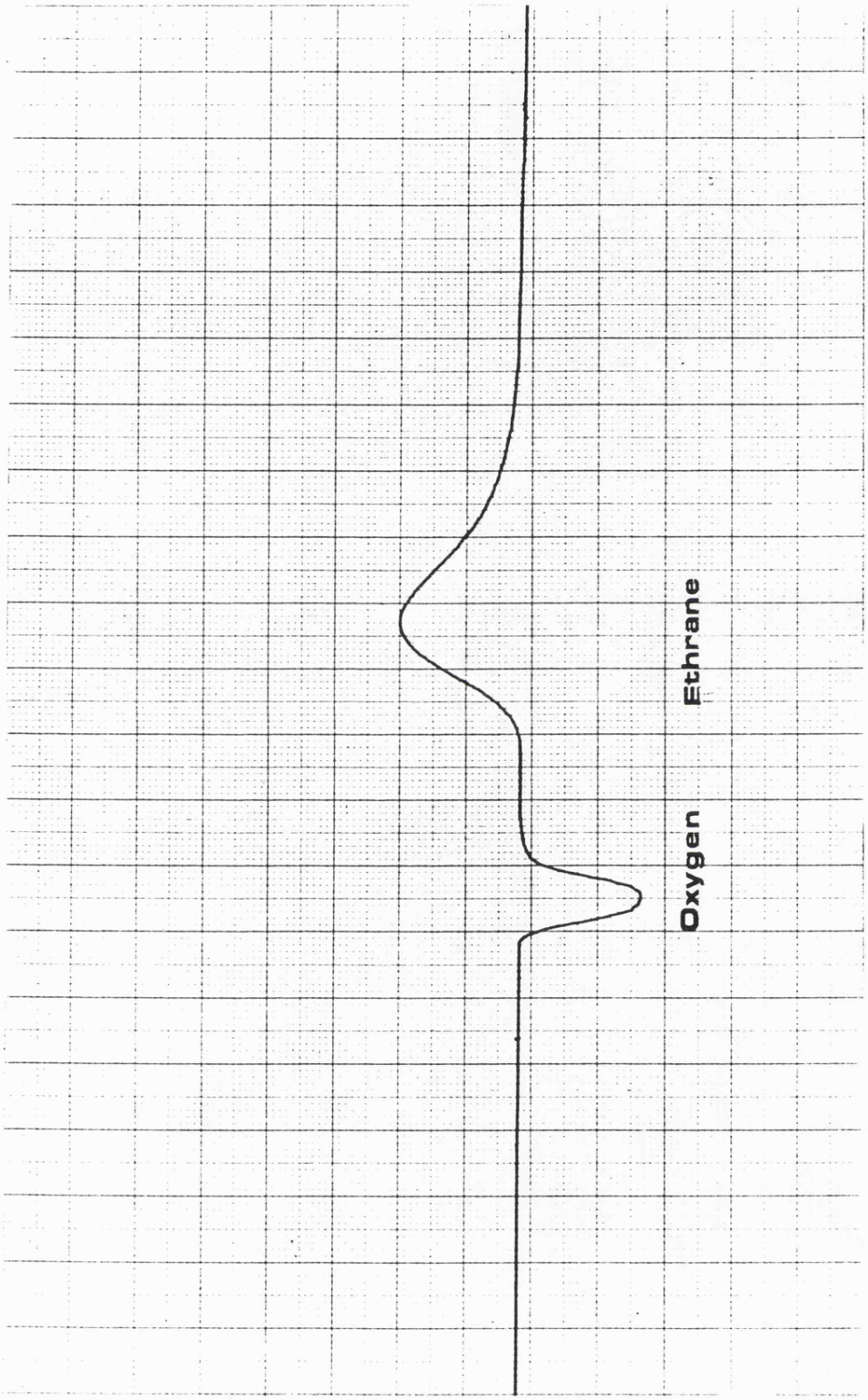


Figure 7.15

at which the peak turns over is well above the halothane peak, the measurement of halothane will be in the linear range.

Oxygen was also separated from ethrane and penthrane (as shown in Figures 7.15 and 7.16). These anaesthetics were not picked out for any particular property. It is expected that other anaesthetics would be similarly separated with the possible exception of cyclopropane, which is the lightest and, at normal temperatures and pressures, the only gaseous potent inhalation agent used.

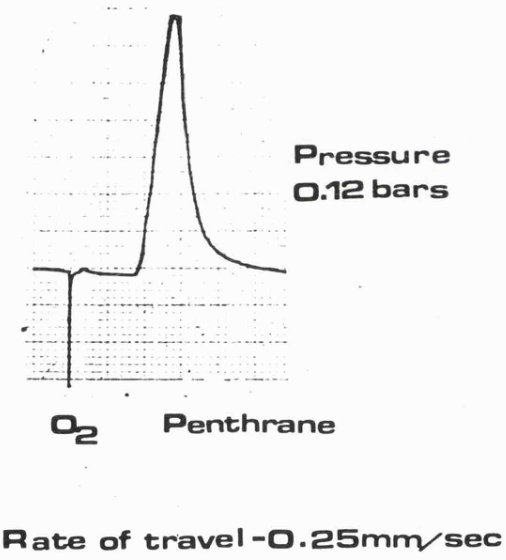


Figure 7.16

7.8 Repeatability

Figure 7.17 shows 3 injections of sample introduced automatically by the sampling system electronics. Peak heights and shape are the same. A 40 cm column with a carrier-gas flow-rate of 2000 ml/min was used.

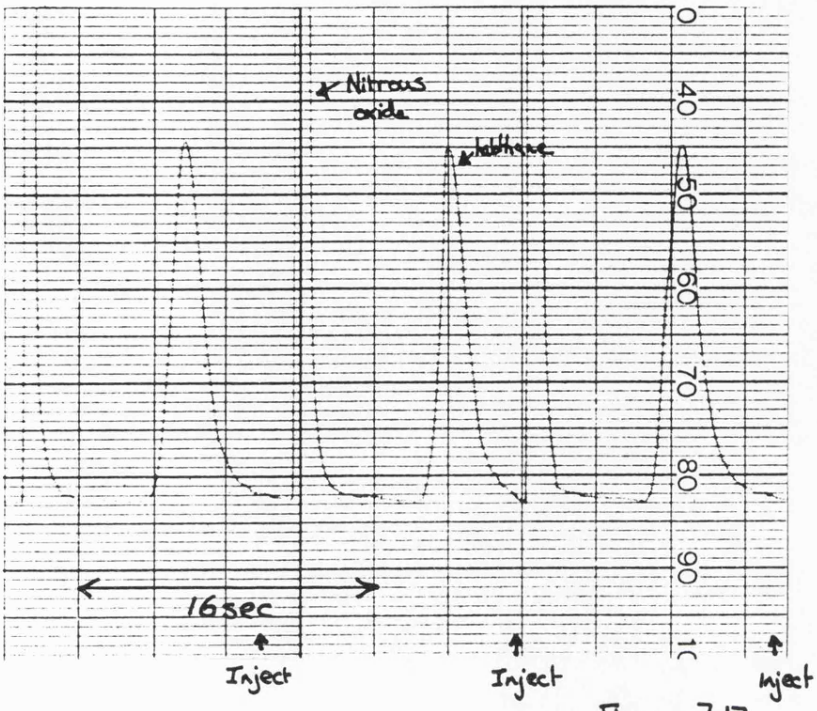


Figure 7.17

It should be noted that no experiments were carried out to determine the long term stability of the detector. A wide range of amplitude variation is available depending on the setting up of the detector. It is envisaged that the detector would be set up initially and the adjustment then sealed. Electronic scaling of the output would be provided.

7.9 System Parameters Selected

The solenoid operated gas sampling valve was satisfactory as was the detector system as far as was proven. A column 40 cm long, filled with Chromosorb W NAW coated with 15% by weight Kel-F-Oil, with an air carrier-gas at a flow rate of 2000 ml/min gives a satisfactory separation.

Having made this selection we can determine the proportion of nitrous oxide and halothane in the gas phase at equilibrium.

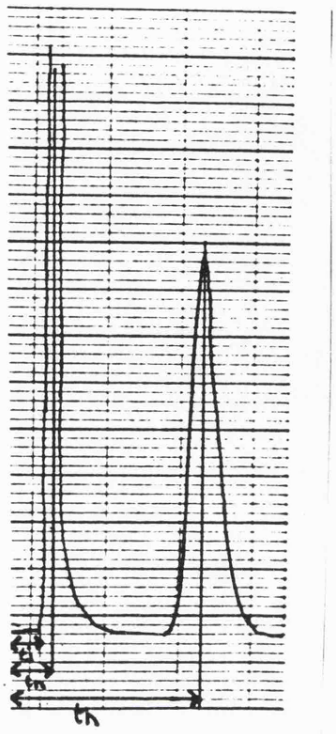


Figure 7.18

From the equations derived in Chapter 6 particularly that $R = \frac{N}{\phi}$ equation 15 which states that the volumes of gas that must be added (R) before a particular peak is eluted is the number of plates (N) divided by the proportion of the substance in the gas phase at equilibrium (ϕ).

If the column is short and the leading edge of the first peak is sharp, then the time from injection to the start of the peak (t_i) gives an indication of the number of plates in the column, since the peak can only start to emerge after N volumes of gas have been added.

$t_i = kN$ where k is the constant of proportionality which converts N into units of time. Similarly $t_n = kR$ where t_n is the time from introduction to the nitrous oxide peak, thus

$$R = \frac{N}{\phi}$$

becomes $$\frac{tn}{k} = \frac{ti}{k\phi_n} \Rightarrow \phi_n = \frac{ti}{tn}$$

where ϕ_n is the proportion of nitrous oxide in the mobile phase,

and

$$\mathcal{Z}_h = \frac{ti}{th}$$

where $\mathcal{Z}_h$ is the proportion of halothane in the mobile phase, and th the time from introduction to the halothane peak.

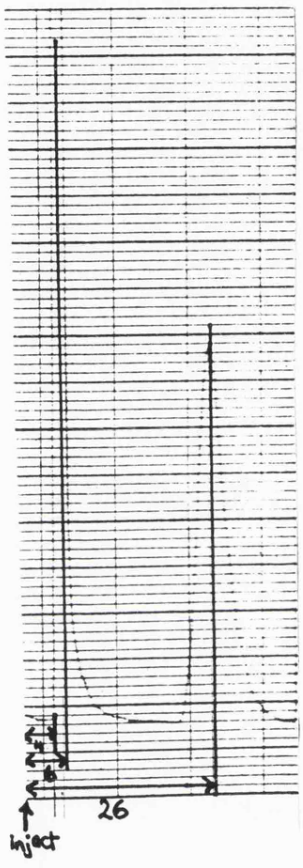


Figure 7.19

Thus from Figure 7.19

$$\mathcal{Z}_n = \frac{4}{6} = 0.67$$

$$\mathcal{Z}_n = \frac{4}{26} = 0.15$$

This is only approximate due to the difficulty of measuring the start of injection.

7.10 Review

It has been shown that the gas chromatographic system described could form the basis of a practical universal anaesthetic monitor.

Chapter 8

8. Work Required to Produce a Clinical Instrument

There are various areas in which work is required, each will be covered separately.

8.1 Carrier Gas Supply

In the laboratory it was satisfactory to use a bottled supply. The final instrument will require a method of providing a steady flow at 2000 ml/min from the operating theatre atmosphere.

8.2 Sample Valve Electronics

This needs some modification as the circuit used is over elaborate. It provides facilities that would not be required in the instrument where a fixed repetition rate and time of sample introduction will be used.

8.3 Detector

No work has been done on the stability of the detector. The base-line seems to be reasonably free from drift, but it is important that the detector should be thoughroughly investigated.

8.4 Timing Circuit for Peak Detection

This needs to be developed so that the peak of interest may be selected and its height measured.

8.5 Physical Arrangement of Components

Care must be taken with the physical arrangements of the components. The column may be made into a U shape with the arms vertical. This will prevent the column material settling and leaving a gap running the whole column length, as could happen if the column was mounted horiz-ontally. The column should be as close as possible to the gas sampling

valve and the detector in order that band broadening of the elutant is not caused.

The inlet for the carrier gas should obviously not be close to the exhaust from the machine or any other source of contaminated air.

Care will be required to ensure that the machine is easy to use, and has appropriate controls.

8.6 Review

Most of the work indicated will be quite easily accomplished. The only area where difficulties may be experienced is the setting up and checking out of the detector. It is believed that the Zeiss refractometer used in the laboratory model is no longer commercially available, so a substitute needs to be found.

Chapter 9

9. Conclusions

This chapter draws together the conclusions reached individually in the various sections.

Initially it was shown that there is a need for an anaesthetic concentration meter if the fully-closed anaesthetic circuit is to be used. The advantages of the fully-closed circuit in reducing theatre pollution, and saving in anaesthetic expenditure were discussed.

The requirements for such an instrument were examined, and the main conclusions being that the meter should respond only to the potent anaesthetic, it should be safe and reliable.

Available meters were examined and the conclusion drawn that none were suitable for routine use with a variety of anaesthetic agents, with the possible exception of the Emma (an instrument made by Engstrom). Thus, as there was no meter proven, it was necessary to develop such an instrument.

Possible methods using physical variables directly were examined, but there was no method found which could distinguish the anaesthetic agents without interference from the other anaesthetic circuit gases.

Separation of the gases were examined. Those methods which involved filtering out of the unwanted components were rejected because eventually the filter would saturate, and conscientious maintenance would be required to avoid falsely low readings being given. The most likely method of separation appeared to be gas chromatography. However, in its usual mode of operation gas chromatography utilises high temperatures and takes a considerable time for a separation. If it were to be used in this application, the separation would need to be accomplished within seconds and at room temperature. It was found that by suitable choice of column material, column length and carrier-

gas flow-rate, a separation of the anaesthetic from the other gases in 15 seconds with a variety of anaesthetic agents could be achieved.

The system developed used a solenoid operated gas sampling valve and a refractometer detector. The column chosen to give a separation, with return to base line between peaks in 15 seconds, was 40 cm long and filled with Chromosorb W NAW coated with 15% Kel-F-Oil. The column is to be operated at 30 ^{o}C with air as the carrier gas.

The modifications that would be required to change the laboratory model developed into a clinical instrument are discussed. Particularly the need to determine if the refractometer is commercially available and whether its stability is satisfactory must both be considered.

The conclusion is drawn that the use of the system developed could form the basis of a practical anaesthetic concentration meter.

Appendix A

Suitability of rubber, plastic, etc for use with halothane

Resistant	Non resistant
Aroldite	Most natural rubbers
Blackol	Cork agglomerates
Some leathers	Leather treated with
Melamine form -	substances like
aldehyde mouldings	stearic acid
Urea form -	Plasticized PVC
aldehyde mouldings	Synthetic rubbers
Polythene	Neoprene (was the
Nylon (only some grades)	best synthetic
Polyterafluoroethylene	rubber tested)
(PTFE)	Perspex
Regenerated cellulose	
Resistol	

Appendix B

Effect of wet halothane on metals

Metal	Type of Attack	Rate	Suitability
Aluminium	White glutinous deposit	Rapid	Unsuitable
Brass 60/40 Cu/Zn	De zincification	Slow	Unsuitable
Phosphor Bronze	None	-	Suitable
Aluminium bronze	Slight green coating	Very slow	Unsuitable for good finish
Hunt & Milton bronze	Slight green coating	Very slow	Unsuitable for good finish
Chromium	None	-	Suitable (plating must be fault free)
Copper	None	-	Suitable
Deoxidise copper	None	-	Suitable
Lead	Decolourisation and incrustation	Rapid	Unsuitable
Magnesium	White incrustation	Rapid	Unsuitable
Magnesium (Chromium treated)	White incrustation	Rapid	Unsuitable
Monel metal 70/30 Ni Cu	Faint white coating	Very slow	Suitable
Nickel	None	-	Suitable

Silver	None	-	Suitable
Stainless steel	None	-	Suitable
Tin	Grey yellow incrustation	-	Unsuitable
Titanium	None	-	Suitable

Inert Support		Liquid Phase		Column		Temperature			Carrier		Detector	Elution Time	Reference
Type	Particle Size.	Type	%	Length	dia	Injection	Column	Detector	Type	Flow Rate			
Sterchamol	0.20-0.25 mm	Apiezon K	25	1.5m	3mm	160°	80°	-	Nitrogen	0.47ml/sec	Flame ionization	Halothane 3 min	Gelbicova 1972
Sil-O-Cel	52-60 mesh	Dinonyl phthalate	15	2'	¼"	-	75°	-	H_2	20ml/min	Thermistor	Halothane 2 min	Adlard E.R. 1960.
Tide	48mesh	-	-	18'	¼"	-	100°	-	He	20ml/min	-	Halothane 3 min	Leibrand R.J. 1967
Chrom P	60-80 mesh	Silicone Fluid MS550	-	6'6"	0.062"	-	88°	-	Air	650ml/min	Flame ionization	Halothane 85 secs	Wortley D.J. 1968
Universal B	60-80 mesh	MS 550	15	-	-	-	60°	-	N_2	75 ml/min	Electron capture	3 min	Davies D.D. 1978
Chromosorb	-	Squalane	5	50cm	-	-	5°	-	-	696cm^3/min	Katherometer	16 sec	Chenceau M. 1963
Celite	80-100 mesh	MS 550	10	12"	¼"	-	30°	-	H_2	45ml/min	Flame ionization	Halothane 4 mins	Butler R.A. 1961
Silicone Rubber Wet Glass Wool	-	-	-	2' 1'	-	60°	Room	150	H_2, N_2 Air	-	Flame ionization	-	Lowe H.J. 1964
Chromosorb 105	60/80 mesh	-	-	2.5m	4mm	-	60°-160° 15°/min	-	-	40ml/min	Flame ionization	Halothane 9mins	Maci U. 1976
Chromosorb NAW	80-100 mesh	Kel F Oil	15	50cm	4mm	-	Room	40°	H_2	70.6cc/min	Thermal conduct'y	Halothane 2 mins	Patzelova V. 1971
Porapak Q	100-120 mesh	-	-	270cm	4mm							6 min	

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